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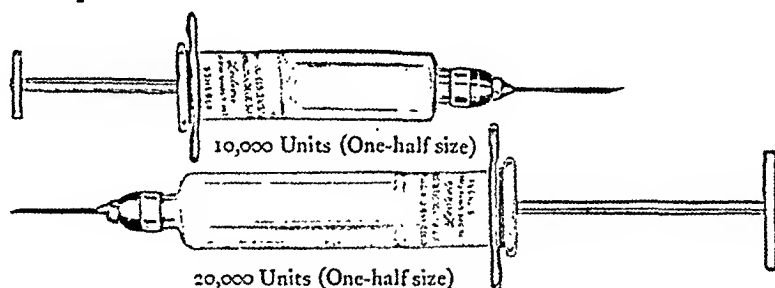
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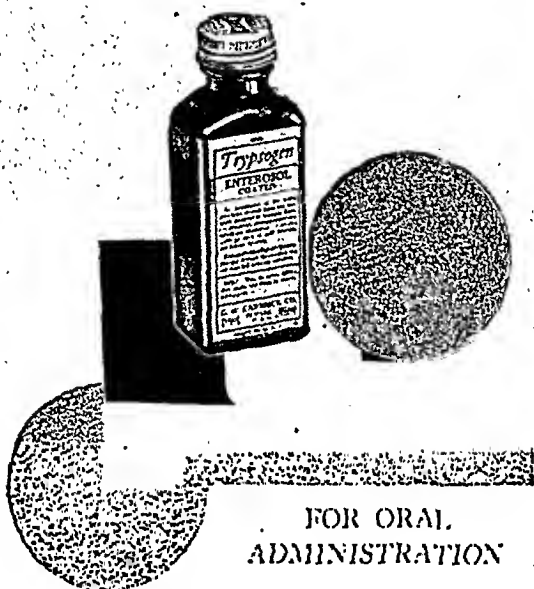
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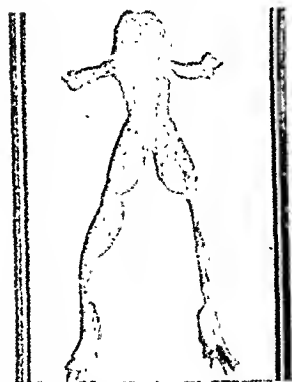
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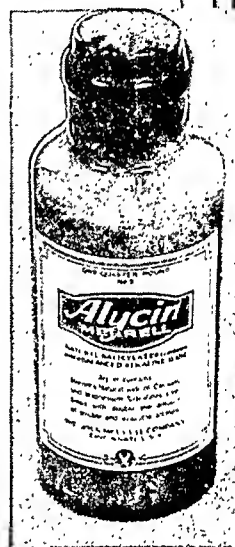
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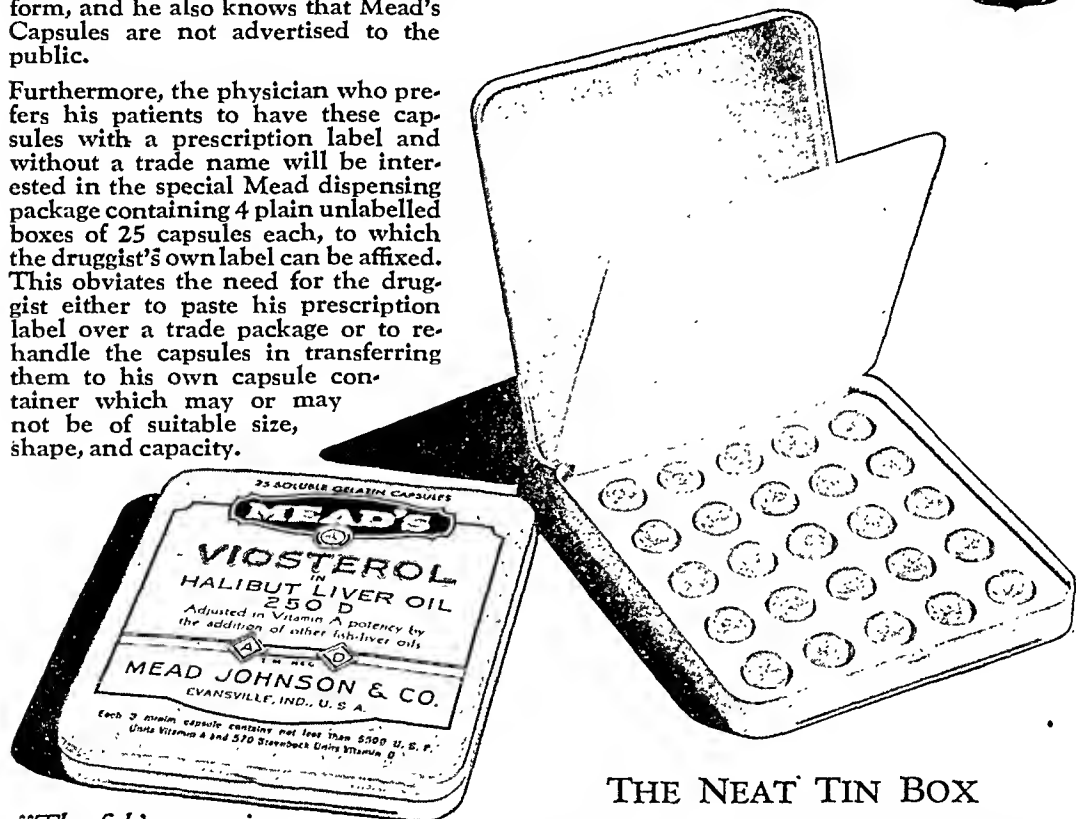
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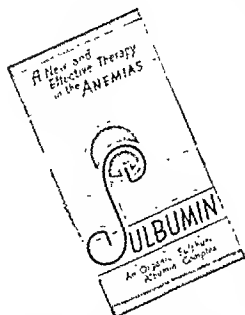
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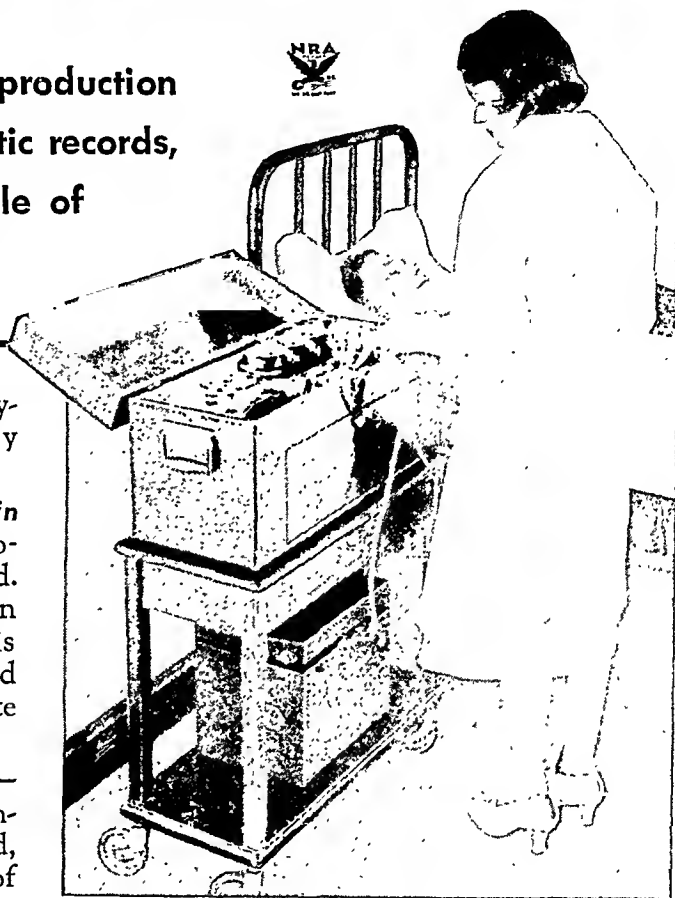
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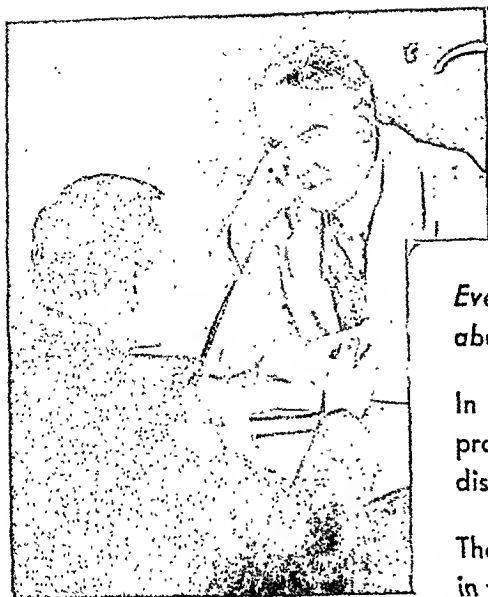
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ORIGINAL ARTICLES.

DISEASE OF THE CORONARY ARTERIES WITH A CONSID-  
ERATION OF DATA ON THE INCREASING MORTALITY  
OF HEART DISEASE.\*

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AND

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DIFFERENT diseases occupy the center of the stage at different times. In my early days in medicine typhoid fever was of paramount interest. Its conquest achieved in the course of a few years—one of the greatest triumphs of medicine—brought another disease into the limelight, namely, tuberculosis. Tuberculosis has now fallen low among the causes of death and bids fair within the lives of persons now living to join the list of deceased diseases. Pneumonia, never far removed from the center of the stage, has not greatly changed its position in the last half century. For the aged it is still the Captain of the Men of Death, but in youth and middle life it is perhaps less of a menace now than formerly. What occupies the center of the stage to-day? Undoubtedly heart disease.

Everywhere heart disease has leaped to the top of the list of causes of death and this is only in part due to the lowered mortality from other diseases. The actual increase in deaths from heart disease, however, in reality represents a triumph of preventive medicine. Young adults are escaping the ravages of tuberculosis and of occupational diseases. More are now living to the age period beyond

\* Read by invitation before the Medical Society of New Jersey, Atlantic City, N. J., June 8, 1933, by the senior author.

40 when heart disease, vascular degeneration and cancer prevail. By the prolongation of the average span of life, to 59 years as it now is, more individuals are kept alive to die in the higher age groups from those diseases that afflict advancing years. It should be mentioned that C. F. and N. W. Bolduan<sup>1</sup> seek to show that the "appalling increase" in heart disease is fictitious. The registered increase in heart disease is, they believe, merely due to a change in terms used in death certificates, such conditions as apoplexy, Bright's disease and senility frequently being listed as heart disease. I cannot feel that this is the correct, certainly not the complete explanation. The tables I have gathered from various sources\* are so concordant that one must conclude there is an actual and not merely a relative increase of deaths from heart disease (Table 1).

TABLE 1.—INCREASING MORTALITY FROM HEART DISEASE (HEALTH DEPARTMENT OF NEW JERSEY).

Age periods.	(Rates per 100,000 Population.)	
	1922.	1932.
30 to 39 . . . . .	8	10
40 to 49 . . . . .	13	19
50 to 59 . . . . .	24	38
60 to 69 . . . . .	39	56
70 to 79 . . . . .	41	62
80 to 89 . . . . .	21	30
90 and over . . . . .	2	5

It should be borne in mind in considering these figures that the rates are based upon total population and that the percentage of the population in the given age groups for 1932 may vary considerably from the percentages for 1922.

TABLE 2.—INCREASING DEATHS FROM HEART DISEASE IN CERTAIN AGE GROUPS IN DETROIT.

	(Rates per 100,000 Population.)			
Age groups.	1923.		1932.	
	No.	Rate.	No.	Rate.
Under 5 . . . . .	22	18.7	13	9.3
5 to 9 . . . . .	21	22.5	11	7.8
10 to 14 . . . . .	31	42.8	21	16.5
15 to 19 . . . . .	26	34.9	24	20.5
20 to 24 . . . . .	46	39.8	28	19.4
25 to 29 . . . . .	51	36.8	48	29.6
30 and over . . . . .	1374	314.0	2416	364.0

The Detroit statistics show the same thing. They demonstrate a tremendous falling off in deaths from heart disease in the early years of life up to 29. After 30, however, there is a much heavier toll now than a decade ago—364 per 100,000 as against 314 (Table 2).

\* Dr. Dublin, of the Metropolitan Life Insurance Company, Dr. Lehrfeld, of the Department of Health of Philadelphia, and Dr. Mahaffey, of the Health Department of New Jersey, have kindly furnished us valuable data.

The following table gives the relevant statistics for Philadelphia:

TABLE 3.—PHILADELPHIA DEATHS FROM HEART DISEASE—1923 TO 1932.

Year.	Total deaths.	Rate per 100,000 population.	Under 10 yrs.	10 to 20 yrs.	20 to 30 yrs.	30 to 40 yrs.	40 to 50 yrs.	50 to 60 yrs.	60 to 70 yrs.	70 to 80 yrs.	80 to 90 yrs.	90 to 100 yrs.	100 and over.
1923	4580	245.3	79	116	134	269	464	819	1122	1028	480	66	3
1924	4349	231.4	77	134	143	218	448	788	1035	996	455	53	2
1925	5097	269.4	53	135	184	288	531	898	1242	1143	544	78	1
1926	2937	311.7	55	101	182	291	648	1027	1566	1387	586	89	5
1927	4762	248.4	56	106	139	279	508	844	1214	1098	446	69	3
1928	4394	227.7	56	80	120	258	485	809	1113	975	451	46	1
1929	4418	227.5	63	103	148	230	441	823	1089	1019	433	68	1
1930	4454	228.0	40	75	132	223	452	806	1132	1091	443	59	1
1931	4363	221.9	33	50	118	208	420	786	1106	1096	484	59	3
1932	5709	288.5	30	91	125	266	528	1019	1594	1339	631	86	

I do not know how to explain the uniformly high figures after 40 for the year 1926, unless one attributes it to the prevalence of acute respiratory infections during that year, since statistics show that such infections influence the death rate from other diseases unfavorably. Very striking is the increase of 1932 over 1931. In England and Wales there seems also to be a steady increase in deaths from heart disease since 1921, but with an encouraging decline in 1931 and 1932.

To sum up: Whether there is or there is not an "alarming increase" in deaths from heart disease, the fact is that heart disease stands at the head of the list. This makes it a definite problem in health conservation in the sense that efforts should be made to postpone as late as possible death from those degenerative diseases among which that of the heart and bloodvessels is the most important. Degeneration is the price of old age and mankind prefers to pay that price as late as possible. From a detached biologic point of view this may not be a desirable aim—an old tree bearing no fruit or only a few green leaves had better give place to a younger one—but society today with its humane instincts seeks to keep alive the cripple as well as the lean and slippered pantaloons.

I shall not go into the history of coronary occlusion. Nearly everyone who writes exhaustively on the subject finds as he proceeds an earlier reference than his literary predecessors. I believe, however, that I have discovered the earliest recorded case—and yet some future writer may find an earlier one. In Homer's *Odyssey*,<sup>2</sup> it is stated that Phoebus Apollo shed down his gentle darts upon Phrontis, son of Onetor, Menelaus' navigator, and "he dropped dead with the steering oar of the moving ship within his hands." This impresses me as an instantaneous painless coronary death.

No one in recent years has contributed more to our understanding of the subject of coronary disease than J. B. Herriek of Chicago. Credit also belongs to George Dock, E. R. LeCount and many others. The first case of coronary thrombosis diagnosed during life as far as I have been able to ascertain, was reported by Hammer<sup>3</sup> who had observed it in 1876. It was confirmed at autopsy although the pathologic description is not very clear. Hammer incidentally cites a sentence from Cohnheim written in 1877 which shows the fallacy of prophecy. "It is a fact that Bezold through experimental closure of a coronary artery was able to bring the heart to a stop. Whether, however, a similar phenomenon will ever be observed in human pathology seems to me very improbable."\*

Not much space need be given to a consideration of the causes for the simple reason that we know so little about them. We can say under what conditions coronary disease may occur but that is far removed from explaining its etiology. Coronary disease, particularly coronary thrombosis, prefers the male sex between the ages of 50 and 70, although it may occur much earlier. Smith and Bartels<sup>4</sup> report 2 cases and collect 20 from the literature of ages from 12 to 40. Coronary occlusion is more common in private than in charity hospital practice, indicating that social status is a factor. High blood pressure is an important element, but typical cases occur also in persons with low blood pressure. Syphilis, strange to say, is not a significant factor either in my personal experience or in the literature. It is important only when it produces atresia of the coronary ostia by extension from the aorta. Diabetes is by many considered an important factor (Nathanson<sup>5</sup>), although in my own series it does not appear to play a conspicuous rôle. Nephritis, thromboangiitis obliterans and polycythemia rubra play their part. An embolus derived from a mural thrombus or rarely from a diseased valve may also cause occlusion.

That polycythemia through inspissation of the blood might favor coronary thrombosis is theoretically possible and has been demonstrated in 1 of my cases. (See also Boyd.<sup>6</sup>)

That infectious diseases in earlier life may play a rôle is a possibility that needs further investigation.

Heredity was an apparent factor in 27 per cent of my own cases of coronary disease. But in what heredity consists, whether it merely predisposes, the environment doing the rest, or whether it carries on through generations the actual elements of the disease, we do not know. Heredity and the closely related constitution are subjects in which as far as any real knowledge is concerned we are still, to use Dean Brown's phrase, in the Desert of Moab. Habits, such as a too sedentary or too athletic mode of life, are also possible agents but as they are far more widely prevalent than is coronary disease,

\* Those interested in the history of coronary disease will find a fairly complete account in Warburg's articles (*Acta med. Scand.*, 1930, 73, 425).

some additional factors must be operative and that X factor is perhaps the inherited constitution. Whether that is something chemical or something anatomic remains to be discovered.

Regarding habits, I believe that worry is one of the most effective in producing the coronary syndrome; overeating, overindulgence in sexual relations, especially if these are not accompanied by complete gratification, overambitiousness, also are prominent in the histories of coronary cases if we but search for them. The alcoholic habit of itself, if not a by-product of the others mentioned, does not seem to me to lead to coronary disease. I cannot give the same clean bill of health to tobacco. One-fourth of the patients with coronary occlusion that I have seen were heavy smokers. Here again it must be admitted that not all who smoke to excess become victims of coronary disease but the number that do is sufficiently large to make me rank tobacco definitely among the causes.\*

Acute coronary closure may be precipitated by any unusual physical effort, by emotional excitement,† during coitus, during public speaking, through fatigue after an arduous journey or from play, or by any trying experience.‡ Sometimes, however, no immediate exciting cause is discoverable. When the attack occurs during sleep I have thought it possible that a harrowing nightmare was the *agent provocateur*. MacWilliams has shown that the blood pressure may rise 20 to 30 mm. during dreams or uneasy sleep.

There is no physical or bodily habitus characteristic of patients destined to have coronary disease. Perhaps the stocky, short-necked, overweight, hypertensive individual predominates but the slender and spare are not exempt. Many have tortuous temporal arteries and arcus or annulus senilis. The radial arteries may be soft but in many instances they are thick and leathery, rarely beaded.§ The majority of "coronary" individuals are active and athletic, often passionate golf players, but the disease as I have said occurs among the sedentary as well. The greater proportion are heavy eaters. Many are given to liberal night suppers, and the excessive use of tobacco is a common habit.

As coronary anastomoses are said to be richer in persons of advanced age, it is not surprising that individuals over 70 rarely die of coronary occlusion (Barnes<sup>9</sup>).

\* The work of Sulzberger and Harkavy<sup>7</sup> shows that many persons have tobacco sensitiveness. Harkavy found 13 patients among 36 suffering from coronary artery disease sensitive to tobacco by skin tests. The average age of the patients who reacted to tobacco was 45 years; the average age of coronary patients who failed to react to tobacco was 60 years.

† As John Hunter said over a century and a half ago—"My life is in the hands of any rascal that chooses to plague me."

‡ Fitzhugh and Hamilton<sup>8</sup> believe that drugs, such as thyroid extract, may bring on an attack; insulin and adrenalin may also do so.

§ It should be borne in mind that soft radials are no proof that the arterioles of the heart or of the brain are normal—they may be in a state of advanced sclerosis.



*Symptomatology.* The symptoms of acute sudden closure of a coronary artery of considerable size are dramatic in the extreme. The patient, usually a man past 50, florid, thick-necked and heavy-set, is seized suddenly with an unendurable pain, in its fearful severity unlike anything he has ever experienced before. His face becomes ashen or bluish-gray, exsanguined and pinched. A cold sweat breaks out over his body, the extremities become cold, the pulse small and thready, and usually rapid although sometimes it is slow. In certain cases no pulse is obtainable. The patient is apprehensive to the highest degree; he is sure death is in the offing. He may lose consciousness and may have a convulsion. The heart sounds are feeble, the first sound at the apex scarcely audible; frequently a systolic murmur not heard before is found at the mitral area or over the body of the heart. Respiration is shallow and restricted; there may be shortness of breath and air hunger; sometimes the breathing is of the Cheyne-Stokes type. Râles may be heard over the bases of the lungs: sometimes pulmonary infarction occurs with spitting of blood. The blood pressure usually drops precipitously, sometimes to a point when none is obtainable by the auscultatory method. I have seen it fall from 220 systolic to 90 in the course of a few hours in a patient who nevertheless recovered.

The pain is of a crushing, crunching or tearing character and is situated usually behind the middle or lower sternum, or in the region of the parasternal lines on both sides of the chest, or in the epigastrium, or even in the umbilical region. It is, as a rule, stationary, but it may radiate into one or both arms, to the lower cervical region in the back or up into the jaws. In several of my cases the pain in the left elbow was more severe than the substernal pain.

The attack may be accompanied by vomiting and marked abdominal distention, so that it closely resembles an acute abdominal catastrophe such as perforation of a peptic ulcer, biliary colic, acute pancreatitis, mesenteric thrombosis or the gastric crises of tabes.

As the outstanding features are those of shock, the temperature is low in the beginning but it soon starts to rise to 100° F. or higher, rarely above 103°. This is probably a protein fever caused by the absorption of degradation products from the infarction in the heart. To the same cause is to be ascribed the leukocytosis that appears soon after the onset of the thrombosis. Libman has detected it as early as 1½ hours after the commencement of an attack. It usually ranges between 12,000 and 20,000 but may reach as high as 30,000. If the leukocytosis persists or increases in the absence of a complication it is indicative of progressive necrosis of the heart wall which may lead to cardiac rupture or to aneurysm. In some cases, especially if the obstructed artery is the anterior coronary, a small patch of pericardial friction, corresponding in all probability to the area of infarction, can be detected; at times the pericarditis extends far beyond the infarcted area. Enlargement of the liver is indicative,

in the early stages before any congestive heart failure has taken place, of closure of the right coronary artery. In such cases slight jaundice may occur. Albuminuria is usually present and in rare cases sugar has been found in the urine.

I have said that the patient is panic stricken by fear of death yet I have seen individuals who although convinced of the close approach of death, were never emotionally or psychically paralyzed with fear. They realized that their time had come but were unafraid.

While the picture I have sketched is perhaps the most common, it is not the invariable one. Coronary occlusion may cause instant death without any preliminary pain. Such apparently painless deaths are not uncommon on the golf links and in other public places. Sometimes if the patient has had a little bloating and belching of gas before, the death is attributed, at least in the newspapers, to acute indigestion. It is of course impossible when confronted with an instantaneous death to be sure before the autopsy of what has actually taken place—whether there is a coronary obstruction or whether death was due to angina pectoris without obstruction.\* This goes to show how closely the two conditions, coronary thrombosis and angina pectoris, are allied. What is commonly called “status anginosus” is most often a progressive coronary occlusion and not simply cumulative attacks of angina pectoris. In the acutely fatal cases there is no time, even if a thrombus is present, for infarction to form.

In some cases after a 24- or 36-hour period of profound collapse during which life seems to hang by a thread, the patient being perhaps in a stupor, there is a sudden improvement in the symptoms, giving rise to the hope that all danger is passed. Such hope, however, is often illusory. The patient while talking or eating may suddenly drop back dead. If one is watchful one can detect in this type of case during the interval of improvement definite signs of grave myocardial damage.

Psychic disturbances are not rare in the severer types of coronary occlusion. They may take the form of confusional and hallucinatory states, of delusions, of acute maniacal outbursts and of attacks resembling delirium tremens. In every surviving case that I have seen the psychosis disappeared completely.

*Larval Coronary Disease.* In addition to acute coronary closure there is a form of coronary disease that does not present a sufficiently striking picture always to be recognized. Anatomically it consists of a gradual narrowing of the coronary vessels due to a progressive endarteritis. The result is a lessening of the blood supply with a consequent oxygen deprivation of the tissues, a condition I have called *histanoxia*. This *histanoxia* may lead to degenerative changes in the muscle fibers and their replacement by fibrous

\* Sudden death has, of course, many other possible causes—apoplexy, rupture of aneurysm, etc.

tissue. Clinically it may manifest itself in various ways. One is the usual type of chronic congestive heart failure. The other is more specifically coronary and presents the following symptoms:

There may be a sense of substernal oppression which, as a rule, is relieved by rest. As belching is not infrequent, patients as well as physicians often interpret such seizures as due to indigestion, an error from which there is a sad awakening, not for the patient, but for the doctor. Attacks of fainting may also be produced by this type of chronic coronary artery disease. And then there are sudden mild attacks of heart failure approaching fainting, with pallor, sweating and great restlessness, but with absence of pain.

Any of the mild forms may without interruption pass into a grave form. Thus in the case of Mr. W. (seen with Dr. H. S. Read) the patient experienced a peculiar empty or vacuum feeling, as he called it, in his chest and soon afterward went into collapse with *angor animi*, falling blood pressure and with electrocardiographic findings of coronary occlusion, although he never had any acute pain. He was compelled to remain in bed for 9 weeks.

Acute pulmonary edema with inky cyanosis may be a manifestation of coronary disease. This condition, in its suddenness and violence, often tests the doctor's resourcefulness and intelligence. The best measures for combating it are: Venesection, morphin and atropin, and, if need be, dry cupping over the chest.

The fluoroscope may give evidence of coronary disease in showing feeble contractions, a see-saw type of contraction (Ernstene<sup>10</sup>). It would seem to be unwise, however, in the early stages at least, to subject the patient to the strain of such an examination. Ernstene<sup>10</sup> points out a lessened vital capacity in cases of coronary disease. In several instances I found absence of the dorsalis pedis pulse as collateral evidence of arteriosclerosis; in a few cases there was a history of intermittent claudication.

**Electrocardiographic Evidence.** *Angina Pectoris.* There are no characteristic changes in the electrocardiograms in patients suffering from angina pectoris during the intervals between paroxysms and in many cases during the attack. In others, however, certain alterations in the ventricular complexes occur. During the paroxysm the *T* waves in Lead I, in Lead II, or in both, may become diphasic or inverted when they are upright between attacks or more deeply inverted if they are already abnormal.\* The severity of the pain does not seem to determine whether or not changes in the electrocardiogram will occur, but the degree of change when present is greater during more severe attacks.

*Coronary Sclerosis.* The electrocardiogram is not necessarily altered in sclerosis of the coronary arteries. Conduction defects,

\* These changes are similar to those seen in electrocardiograms of dogs when branches of the coronary arteries are experimentally occluded and support the theory that during attacks of angina the blood supply of the myocardium is deficient.

however, not infrequently occur. Thus the commonest cause of intraventricular block is coronary disease, and various types of arrhythmia, auriculoventricular delayed conduction, low voltage, and splintering of the *Q R S* complexes are sometimes seen.

*Coronary Occlusion.* In coronary occlusion the electrocardiographic changes vary with the size of the infarcted area and with its position in relation to the plane of the leads employed. The most common site of thrombosis—the descending branch of the left coronary artery, the infarct being near the tip of the left ventricle—gives rise to characteristic changes in the electrocardiogram. Soon after closure of the vessel the *Q R S* complex becomes slurred or decreased or widened and the *T* wave in Lead I takes off high on the downstroke of the *R*, with an initial upward deflection and a terminal depression. Coincidentally the *S-T* interval in Lead III is depressed and the *T* wave inverted. Similar though less characteristic changes occur in Lead II. During the succeeding days the *T* wave in Lead I and often in Lead II becomes deeply inverted, with an elevated *S-T* interval, while in Lead III the *S-T* interval remains depressed and the *T* wave becomes upright. In favorable cases the electrocardiogram may return to normal with repair of the infarct, but often some evidence remains in an altered *S-T* interval or *T* wave in Leads I and III.

In cases where the right coronary artery has been occluded the electrocardiogram shows first a high origin and later inversion of the *T* wave in Lead III, and depression of the *S-T* interval in Lead I.

Thrombosis of other branches of the coronary arteries shows no changes or less characteristic alterations when the conventional leads are used. Thus it has been pointed out recently that an abnormal *Q* wave in Lead III in the absence of right axis deviation is often the only electrocardiographic evidence of occlusion. The use of anteroposterior leads as suggested by Wolferth and Wood,<sup>11</sup> the electrodes being placed directly on the chest, or of multiple leads as employed by Hyman, have shown abnormalities of the *S-T* intervals and *T* waves in a number of cases where the infarct was present in an area "silent" to the usual leads.

**DIFFERENCES BETWEEN ANGINA PECTORIS AND CORONARY THROMBOSIS.** Although at times it is difficult to distinguish between these two, since they are closely related pathogenetically, there are certain differences that should be borne in mind from their importance both in diagnosis and in prognosis. While in all probability angina pectoris is a "coronary affair" to use a French phrase, it may occur in persons who give no evidence by any known test of coronary disease. Pathogenetically it differs from coronary thrombosis in that it is due, so we believe, to a transitory spasm of coronary artery and not to a real plugging of the vessel.

The important clinical differences are indicated in the following table:\*

TABLE 4.—CLINICAL DIFFERENCES BETWEEN ANGINA PECTORIS AND CORONARY THROMBOSIS.

	Angina pectoris.	Coronary thrombosis.
Beginning of attack . . . .	During effort	During rest.
Seat of pain . . . . .	Behind middle of sternum	Behind lower sternum or in epigastrium.
Radiation . . . . .	To left shoulder and down left arm	May be absent.
Dyspnea . . . . .	Not present	Marked.
Behavior of patient . . . .	Quiet	May be restless.
Duration of attack . . . .	Few minutes	Hours to days.
Shock . . . . .	Absent	Present.
Vomiting . . . . .	Rare	Frequent.
Pulse . . . . .	Unchanged or tense	Small, often rapid.
Arrhythmia . . . . .	Rare	In about 15 per cent.
Temperature . . . . .	Normal	Elevated.
Blood pressure . . . . .	Unchanged or rises	Falls or remains stationary.
Heart sounds . . . . .	Normal	Frequently soft; pericardial friction often present; at times gallop rhythm.
Congestive signs . . . . .	Absent	Often present.
Electrocardiogram . . . .	Often normal	Usually characteristic.
Nitrites . . . . .	Useful	No effect.
Leukocytosis . . . . .	Absent.	Present.

**DIFFERENTIAL DIAGNOSIS.** *Pericarditis* independent of coronary occlusion is not often painful but it may be. While one would be likely to conclude that an acute painful *pericarditis* had a thrombotic or embolic infarct as its cause, in young persons and even in the elderly an acute *pericarditis* of infective or uremic origin may be painful and simulate *angina pectoris* or coronary occlusion.

*Pneumothorax.* In 1 case seen in consultation a diagnosis of *angina pectoris* had been made. When I saw the patient some hours after he had been seized he was still suffering severe chest pain. The man was a bunder and the attack had come on while he was at work on a building. Upon examination I found that he had a spontaneous *pneumothorax*.

In another case *herpes zoster* of the thorax produced a picture that had led to a diagnosis of *angina pectoris* or rather of coronary thrombosis. There were only a few papules visible at the time I made my examination, but as they began at the spine and were present in the axilla, the correct diagnosis was readily made.

*Angina pectoris* and coronary occlusion may also be simulated by *myalgia*, *intercostal neuralgia*, *nervous dyspepsia*, and *hysteria*. The hysterical mimicry is illustrated by the following case:

A woman, about 52, a very important member of my early clientèle, whose sister was suffering from *angina pectoris*, began to have similar

\* Modified from Warburg (*Acta med. Scand.*, 1930, 73, 547), Parkinson and Bedford (*Lancet*, 1928, 1, 4; *Heart*, 1928, 14, 195) and Keefer and Resnik (*Arch. Int. Med.*, 1928, 21, 769).

attacks of precordial pain radiating into the arms and having a considerable duration. They usually came on after a domestic scene, a frequent occurrence. I took them to be hysterical. One day while conducting a dispensary clinic I received a message to come at once, as Mrs. D. was having a terrible attack and seemed to be dying. My first thought was, "Have I been mistaken in my diagnosis?" The taxicab seemed to crawl at a snail's pace. As I approached the house I fully expected to see the undertaker's wagon at the door. I rushed upstairs and found the patient sitting by the open window moaning with pain and declaring herself convinced that the end was near. Finding her pulse good and no evidence of shock I tested sensation with a pin and found her completely anesthetic for touch and pain up to the elbows. This lady lived for many years and died eventually from a delayed cerebral hemorrhage (Spätaapoplexie) after an automobile accident.

*Differential Diagnosis from Abdominal Conditions.* As I have said coronary occlusion may closely simulate an acute abdominal accident. The following are the more important:

*Gall Stone Colic.* Although differential diagnosis is sometimes exceedingly difficult, the history of previous substernal oppression, the profound degree of shock, the absence of tenderness in the gall bladder area, the male sex, are useful guides. If fever, leukocytosis and pericardial friction develop the diagnosis can no longer be in doubt. It must, however, be borne in mind that if the right coronary artery is obstructed, there may be a rapid swelling of the liver with tenderness, which might mislead.

In 1 case in which our diagnosis see-sawed between an acute cardiac seizure and a gall stone attack, the patient could only find comfort by getting on all fours. We decided in favor of a cardiac attack but the autopsy revealed a ruptured dissecting aneurysm.

*Mesenteric Thrombosis.* In 1 case coming under my observation the question of the possibility of mesenteric thrombosis arose.

A man in the early forties, who had a history of pernicious anemia from which he seemed to have recovered except for symptoms of combined spinal sclerosis, was seized with sudden sharp pain in the epigastrium with vomiting, blood in the bowel movements, and marked abdominal distention. At autopsy the man had no definite cardiac infarct but a firm antemortem thrombus in the apex of the left ventricle. There was no thrombosis either of the mesenteric arteries or veins.

*Rupture of a peptic ulcer* may resemble acute coronary thrombosis. The diagnosis has to be made on a careful history and on a thorough physical examination.

*A tabetic crisis* may conceivably simulate coronary occlusion. One should always make it a habit in every obscure case of severe epigastric pain to test the ocular and tendon reflexes.

*Acute Pancreatitis.* I have seen 1 case in which it was very difficult at the moment to tell whether the patient had coronary occlusion or acute pancreatitis. The conclusion was finally reached that the man had had some abdominal catastrophe and at operation acute pancreatitis was found.

*Diabetic Acidosis.* It is sometimes very difficult to tell whether a severe chest pang in a patient suffering from diabetic acidosis is or is not due to coronary block. As the use of insulin is dangerous in coronary occlusion, the diagnosis has much more than academic interest. It might be well in a doubtful case to treat the patient with alkalies and orange juice. If the symptoms disappear with lessening of the acidosis, then they were in all likelihood not due to coronary thrombosis.

*Prognosis* is often a more difficult art than diagnosis, and yet the doctor's reputation to a large extent stands or falls by it. In coronary occlusion it is particularly hazardous to venture a prediction as is shown in the 2 following cases:

Mr. H., a Philadelphia merchant, aged 54, who 7 years before had had an attack of angina pectoris, was seized with a violent pain in his chest. He was in Paris at the time. A physician was called who appreciated the gravity of the case and summoned a renowned cardiologist. The latter correctly diagnosed coronary occlusion and in a rather brutal way said to the wife, "Madam, your husband will die." The distracted lady insisted that the family doctor stay all night. The next morning the patient was very much better. The consultant on his second visit was amazed at the man's improvement and turning to the wife said, "Madam, I think I was mistaken. Your husband is going to recover." That night the patient had another violent seizure and died.

The second patient, a man with polycythemia rubra, had a typical coronary attack, with fever and leukocytosis and pericardial friction. Within 2 or 3 days the symptoms had entirely subsided. About a week later, when apparently convalescing, he sat up to eat his lunch and dropped over dead.

It is probable that in both these patients there was a ventricular rupture at the site of the infarction or a sudden ventricular fibrillation.

There are, however, certain features that permit a fairly definite prediction. A persistent tachycardia especially with gallop or other disturbance of rhythm, a continuing fall of blood pressure, unyielding pain, and hyperpyrexia,<sup>12</sup> make the prognosis unfavorable. Great severity of pain is, however, not of necessity a fatal omen. In 1 of my cases morphin utterly failed to control the pain; chloroform held it in check just as long as the patient was under its influence. Nevertheless, the man recovered and lived for a number of years, in fact lived through a second attack and through an attack of pneumonia. A rise in blood pressure is a favorable sign.

Patients that have shown symptoms of coronary disease either of the mild or of the painful type are not good subjects for operation. The mental strain may produce angiospastic disturbance in the coronary circulation and may precipitate an attack, the patient dying on the table or shortly afterward. Hence all operations of election should be avoided.

The earlier we can see these patients the better, but whenever we see them we must recognize the true condition, and not be misled

by the prominence of gastric symptoms. It is in the early stages that much can be done and the catastrophe of sudden occlusion either obviated or postponed to a late period when life no longer is very important. In any patient passed 50 an unaccustomed, uncomfortable feeling behind the sternum coming on during walking or on any physical effort should awaken a suspicion of some cardiac abnormality. True, nothing may be discovered on physical examination, though there is often a slight enlargement to the left, a snappy second aortic sound or a systolic murmur at the aortic area. An elevated blood pressure helps in directing the medical mind in the proper channel. The electrocardiogram may show some abnormality, a change in the *Q* or in the *T* wave. But the experienced and careful clinician does not need that; he reads the writing in the patient.

*Treatment* divides itself into two parts, treatment of the attack and subsequent treatment. That of the attack is more or less stereotyped and presents perhaps but one controversial feature and that is the use of digitalis. I shall refer to this in a moment. The following is an epitome of the treatment of the attack.

Absolute rest, mental and physical, the most absolute conceivable. It may be inadvisable to undress the patient at the outset. He should have no company and should not be allowed to talk. He should of course use the bed pan and urinal and should have a night and a day nurse when the circumstances permit. External heat should be applied.

For the relief of pain nothing compares with morphin in large doses. When morphine fails hardly anything else is likely to be successful, although in two instances I have applied leeches to the precordia and found that the pain immediately abated. Nitroglycerin is contraindicated and yet patients sometimes take it because they have been in the habit of using it for attacks of angina pectoris. If the heart should stop suddenly and the doctor is at the bedside, he might resort to an intracardiac injection of 1 cc. of adrenalin chlorid 1 to 1000 solution. Under ordinary circumstances adrenalin and probably ephedrin are contraindicated in patients with angina pectoris and coronary occlusion. The dangers of the use of adrenalin in angina pectoris and coronary sclerosis have been pointed out by Levine, Ernestene and Jacobson,<sup>13</sup> and by Cottrell and Wood.<sup>14</sup>

Another agent of value in my experience is glucose or sugar. The glucose can be given intravenously. I have been in the habit of ordering ginger ale, water-ice, apple sauce, pineapple juice and orange juice for the purpose both of supplying fluid and of supplying sugar.

Levy has recommended oxygen inhalations during the acute attack. I have used them, employing the well-known oxygen tent



for the purpose. The patients were made more comfortable but I have not seen that the procedure had any effect as regards saving life.

A question that nearly always comes up is—Shall digitalis be used? Having in my mind's eye the pathologic condition of the heart in acute coronary occlusion—infarction with softening—I have been afraid of using digitalis in adequate doses and I am glad to see that that is the opinion of most writers. If, however, there is auricular fibrillation or congestive failure as a sequel of the coronary attack then digitalis is indicated as it would be if coronary occlusion had not occurred.

If cardiac stimulation is necessary and very frequently it is demanded, my favorite remedy is caffein sodiobenzoate hypodermically, using an ampule containing 0.5 gm. ( $7\frac{1}{2}$  grains) of the drug. When conditions are less pressing, the caffein sodiobenzoate may be given by mouth in doses of 0.12 to 0.20 gm. (2 to 3 grains).

If diabetes exists insulin should be withheld as it is dangerous in cases of coronary occlusion. Its use would only be justified in threatening coma.

How long should the patient stay in bed? From 5 to 6 weeks is the minimum in a severe case of coronary occlusion. A cardiac scar is thought to be firm after 8 weeks. It may not be wise to tell the patient at the beginning of his incarceration the length of the sentence. The tactful physician will achieve his end by giving an answer which is true but not necessarily specific. The getting-up process should be gradual and so should be the resumption of the ordinary vocations and avocations of life. The man who has had a coronary occlusion should avoid physical strain and should not indulge in competitive athletics. I am also averse to permitting such patients to drive their own cars, although one may have to make concessions in keeping with the patient's circumstances.

The post-thrombotic or interval treatment has been in the main covered in the foregoing section. A few additional suggestions may now be given. Of greatest importance is encouragement. Psychotherapy, of enormous help in most diseases, is of transcendent value in patients who have had anginal or thrombotic attacks.

The diet should be sensible and restricted in quantity if the patient has been habitually a big eater. A little whisky may be allowed to the man who has been accustomed to drinking alcohol.

Drugs are not of much moment. Whether the euphyllin derivatives are of any value in dilating the coronary vessels, as is believed by many or, more properly speaking, is stoutly maintained by the manufacturers, is still a moot question. Until more exact knowledge is available, I shall, however, continue ordering for short periods at a time one or two tablets of metaphyllin or similar product a day. I also believe that small doses of digitalis, 5 or 10 drops thrice daily, are useful.

The patient who has had a genuine attack of coronary thrombosis must ever after shape his life in accordance with his narrowed limitations. He should not exert himself unduly and should cease playing golf, tennis or similar active sports. Short business hours and a long postprandial siesta are very desirable, and a 5-day week is an excellent thing for the coronary individual. If economic conditions permit the patient should take a winter as well as a summer vacation. Many spend their vacations unwisely. Instead of resting they work just as hard only in a different way.

I believe men who have been heavy smokers should reduce their smoking to a minimum or better give it up entirely.

Re-examination at fairly frequent intervals, including electrocardiographic study, is important in discovering any signs of cardiac weakness.

TABLE 5.—PERSONAL CASES OF CORONARY THROMBOSIS.

Number of cases (men 74, women 14) . . . . .	88	Tobacco chewers . . . . .	2
Number of cases living . . . . .	38	Tobacco habits not recorded . . . . .	24
Number of cases dead . . . . .	34	Non-users of tobacco . . . . .	16
Number of cases unknown . . . . .	16	Family history of heart disease or hypertension . . . . .	24
Greatest duration of life after onset of those known to be living . . . . .	16*	No heart disease known . . . . .	41
Greatest duration of life after onset of those known to be dead . . . . .	11*	Definite negative history of heart disease . . . . .	23
Average age of onset (youngest 32, oldest 81) . . . . .	57*	Occupations—men:	
Hypertension (5 blood pressures not recorded) . . . . .	49	Merchants . . . . .	18
Pericardial friction . . . . .	7	Manufacturers or executives . . . . .	18
Typhoid fever . . . . .	7	Physicians . . . . .	10
Renal calculi . . . . .	7	Bankers . . . . .	4
Rheumatism . . . . .	7	Salesmen . . . . .	3
Diabetes . . . . .	4	Clerks . . . . .	3
Syphilis . . . . .	3	Lawyers . . . . .	3
Polycythemia . . . . .	2	Brewers . . . . .	2
Used tobacco (excessively 22) . . . . .	46	Various (1 each) . . . . .	13
Cigarette smokers . . . . .	20	Occupations—women:	
Cigar smokers . . . . .	16	Housewives . . . . .	10
		Nurse . . . . .	1
		No occupation . . . . .	3

\* Years.

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## THE LARGE Q WAVE IN LEAD III OF THE ELECTRO-CARDIOGRAM.

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**I. Introduction.** The following observations are based upon an analysis of 103 electrocardiograms characterized by a normal sinus rhythm with a significant *Q* wave in Lead III selected from records taken in this cardiac clinic during the past 5 years. In addition, there are presented the pathologic alterations in the heart in those cases that came to autopsy. An attempt is made to correlate these lesions with the changes observed in the electrocardiogram.

Pardee,<sup>9</sup> in 1920, published the first analysis of the *R-S-T* interval in a clinical case of coronary occlusion and, at the time, noted a conspicuous *Q* wave in Lead III. This association was again discussed in the first edition of his book<sup>10</sup> and, since then, has been observed by others.<sup>6,12,16</sup> It was not until 1930, however, that Pardee<sup>11</sup> stressed the high incidence of angina pectoris in those patients whose electrocardiograms contained a deep *Q*<sub>3</sub> and emphasized the rarity of this wave in the records of normal, young adults. Further observations on the subject have since appeared.<sup>3,4,14</sup>

That a conspicuous *Q* wave in Lead III is frequently associated with coronary sclerosis and myocardial disease may be seen from the analyses published by various authors. Willius<sup>14</sup> found that out of 300 cases showing this wave, 38 per cent gave a history of angina pectoris and that 89 per cent could be grouped as having angina, hypertension or chronic, non-valvular heart disease. Pardee's series<sup>11</sup> of 43 instances with *Q* waves gave a history of angina pectoris in 63 per cent of the cases, while 77 per cent fell into the group including angina, hypertension and chronic, non-valvular heart disease. Edeiken and Wolferth,<sup>3</sup> in 75 cases, and Ziskin, in 86 cases, found the incidence of angina to be 29 per cent and 14 per cent respectively, while 55 per cent and 65 per cent of the cases fell into the group including angina, hypertension and chronic, non-valvular heart disease.

Although Krumbhaar and Jenks<sup>5</sup> observed a conspicuous *Q*<sub>3</sub> as a common finding in the electrocardiograms of infants between the ages of 2 and 12 months, the rarity of this wave in the records of normal, young adults is evident. In 277 cases with normal hearts Pardee<sup>11</sup> found a large *Q*<sub>3</sub> in only 2 instances. Edeiken and Wolferth<sup>3</sup> in the records of 709 apparently normal college students found none which showed a significant *Q* wave in Lead III. The same authors

examined the electrocardiograms of 117 athletes of the University of Pennsylvania and found a large  $Q_3$  in only 1 case. From the above observations the calculated incidence of a significant  $Q_3$  in the electrocardiograms of normal, young adults is 0.27 per cent.

On the other hand, a conspicuous  $Q$  wave in Lead III has been found to occur in the records of patients who show, in the absence of cardiac signs or symptoms, an elevated diaphragm with lateral displacement of the cardiac apex.<sup>3,11,17</sup> In a small percentage of cases this wave is present in the records of women during the 8th month of pregnancy and disappears after delivery. Similarly, changes in the cardiac axis during respiration occasionally cause, in Lead III, the appearance of a  $Q$  wave which varies in size with the different phases of the respiratory cycle and is frequently associated with flattening or inversion of the  $P$  and  $T$  waves. Ascites, obesity and a wide costal angle all predispose toward a high diaphragm and a transverse cardiac axis. In the average series, the occurrence of this complication appears, at first glance, to be relatively infrequent. However, coronary sclerosis, hypertension and myocardial disease occur commonly in elderly, obese, thick-set individuals. In such cases the influence of lateral displacement of the cardiac apex upon the initial deflection of the  $Q$ - $R$ - $S$  complex in Lead III must be considered.

In summary, then, the accumulated evidence indicates that the deep  $Q$  wave in Lead III is significant as an electrocardiographic abnormality because of its rarity in the records of normal, young adults and the frequency with which it is found in association with heart disease. As a complicating factor, the part played by lateral displacement of the cardiac apex, although usually uncertain in the individual case, would seem to be important.

**II. Analysis of Electrocardiograms.** Out of 3600 patients included in the electrocardiographic examinations for the past 5 years, there were 103 who were over the age of 12, who had complete histories available and whose records were characterized by a normal sinus rhythm with a significant  $Q$  wave in Lead III.

In the selection of significant  $Q$  waves the following standards were used: (1) an initial, downward deflection of the  $Q$ - $R$ - $S$  complex in Lead III; (2) this deflection to be not less than 25 per cent of the greatest excursion of the  $Q$ - $R$ - $S$  in any lead; (3) the downward deflection ( $Q$ ) to be followed by a definite upward deflection ( $R$ ), without a subsequent  $S$  wave; (4) the absence of right axis deviation. These, essentially, are the criteria set down by Pardee in his original article.<sup>11</sup>

The histories of the 103 cases were then studied and note made as to the presence or absence of angina pectoris, hypertension and myocardial insufficiency. In addition, any mention of a syphilitic infection or a previous history of rheumatic fever was recorded. Substernal pain or oppression, brought on by exertion and relieved

by rest or nitrites, was taken as the criterion of angina pectoris. The substernal pain occurring in cases of hypertension or coronary occlusion was included as part of the anginal syndrome. A diastolic pressure of over 100 mm. of Hg in the presence of a systolic pressure above 150 mm. of Hg was taken as evidence of hypertension. Myocardial insufficiency was considered present when, in the absence of other contributing causes, there was moisture at the bases of the lungs posteriorly, edema of the lower extremities, or dyspnea and palpitation with slight exertion.

TABLE 1.—ANALYSIS OF CARDIAC SIGNS AND SYMPTOMS IN 103 CASES SHOWING A LARGE Q WAVE IN LEAD III.

Clinical diagnosis.	Cases.
Anginal syndrome . . . . .	46 (45%)
Hypertension without anginal syndrome . . . . .	19 (18%)
Chronic, non-valvular heart disease without hypertension or anginal syndrome . . . . .	16 (16%)
Absence of cardiac signs or symptoms . . . . .	9 (9%)
Postoperative dyspnea and tachycardia . . . . .	3
Hyperthyroidism . . . . .	2
Neurocirculatory asthenia . . . . .	2
Subacute bacterial endocarditis . . . . .	1
Pneumonia . . . . .	1
Acute rheumatic fever . . . . .	1
Chronic bronchitis . . . . .	1
Syphilitic aortitis with aortic aneurysm . . . . .	1
Syphilitic aortitis with aortic insufficiency . . . . .	1
	<hr/> 103

NOTE.—Of the 103 cases in the present series, 27 were private patients and 76 were seen on the wards or in the clinic. The incidence of angina pectoris in the group of private patients was 59 per cent, while the same symptom occurred in 39 per cent of the ward and clinic patients. The incidence of a positive Wassermann reaction was 12 per cent for the total series and 4 per cent of all the cases gave a history of rheumatic fever.

The comparison of these figures with those obtained by other investigators is seen from the following:

TABLE 2.—ANALYSIS OF CASES WITH LARGE Q WAVES AS FOUND IN THE LITERATURE.

	No. of cases.	Angina pectoris, per cent.	Angina, hypertension, or chronic, non-valvular heart disease, per cent.	Absence of cardiac signs or symptoms, per cent.
Pardce . . . . .	43	63	77	0
Willius . . . . .	300	38	89	1
Edeiken and Wolferth . . . . .	75	29	55	9
Ziskin . . . . .	86	14	65	23
Present series . . . . .	103	45	79	9

III. Associated Changes in the Electrocardiogram. The next attempt, in the present study, was to determine whether or not certain electrocardiographic changes indicative of myocardial damage bore any relation to the incidence of coronary and myocar-

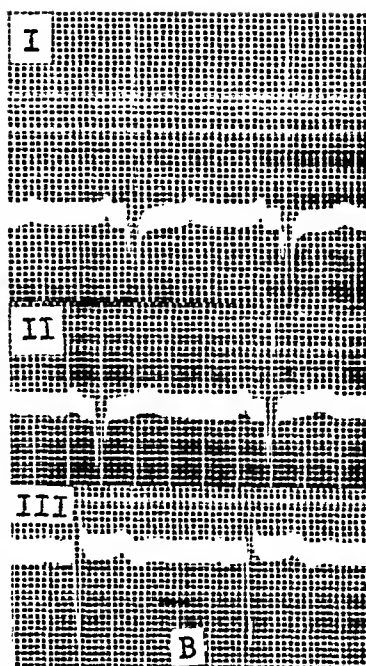
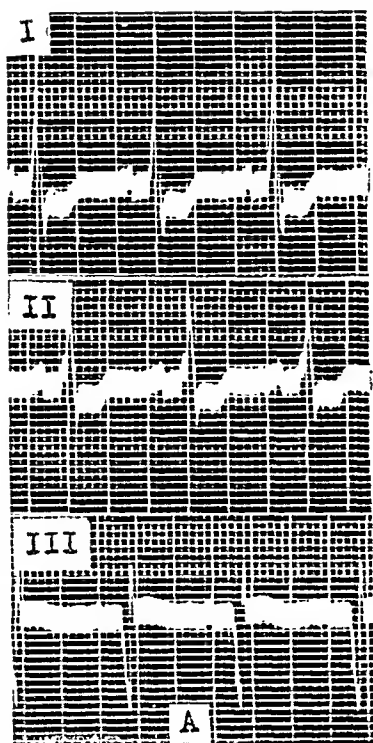


FIG. 1.—Records with large Q waves in Lead III. *A*, syphilitic aortitis with aortic insufficiency and occlusion of the right coronary orifice. Digitalis. Autopsy No. 13000. *B*, a case of angina pectoris with blood pressure at the upper limit of normal. No digitalis.

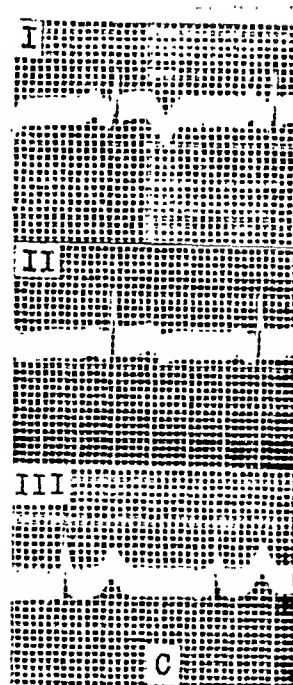
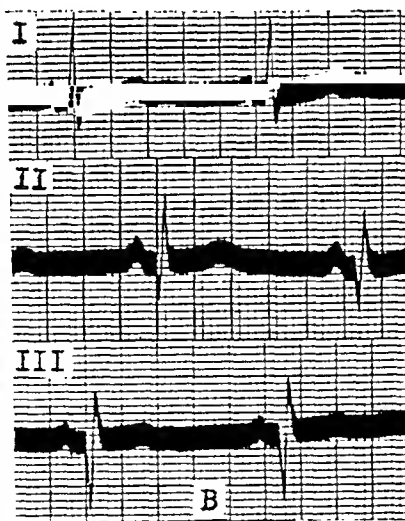
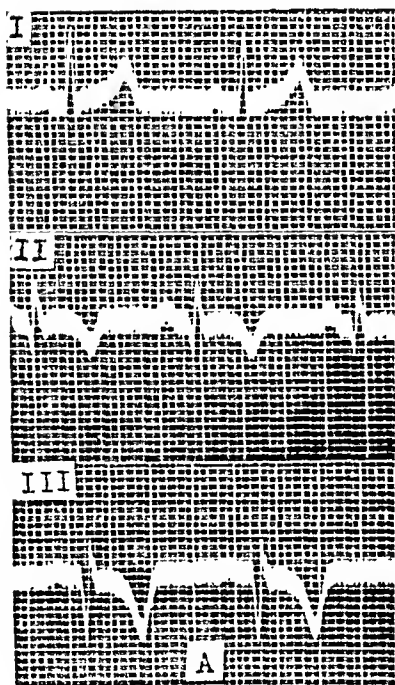


FIG. 2.—Records typical of the three groups of undigitalized patients classified in Table 3. *A*, deep  $Q_3$  with sharply inverted  $T$  waves in Leads II and III. *Group I*. *B*, a large  $Q_3$  in an otherwise normal electrocardiogram. *Group II*. *C*, no  $Q$  wave in Lead III. Sharply inverted  $T$  wave in Lead I and biphasic  $T$  wave in Lead II. *Control group*.



FIG. 3.—Autopsy No. 10888. Heart showing infarction of posterior portion of left ventricle and interventricular septum as the result of posterior portion of right coronary artery occlusion. *LA*, anterior wall of left ventricle; *LP*, posterior wall of left ventricle; *SA*, anterior half of interventricular septum; *SP*, posterior half of interventricular septum; *X-X*, margin of infarct in interventricular septum; *M*, mitral valve.

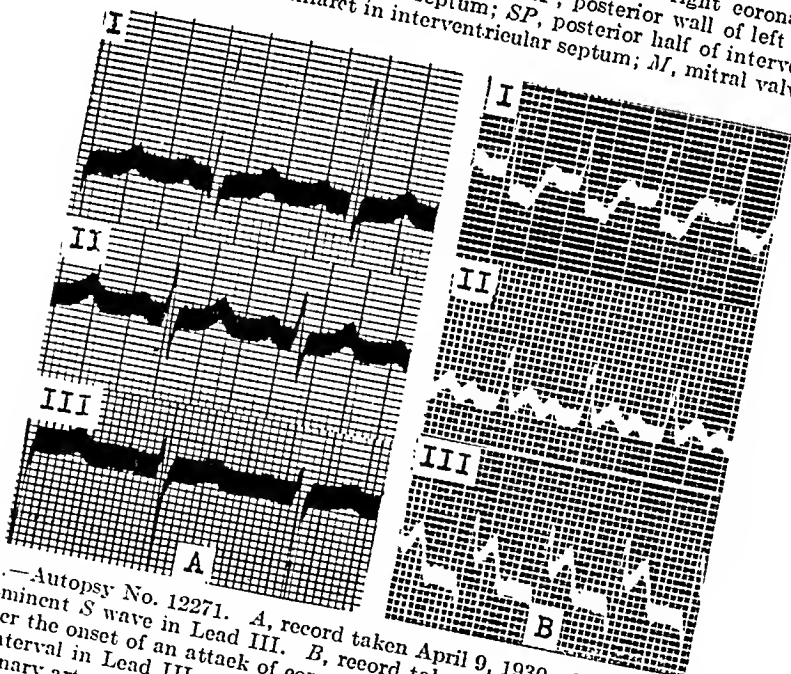


FIG. 4.—Autopsy No. 12271. *A*, record taken April 9, 1930. Left axis deviation with prominent *S* wave in Lead III. *B*, record taken November 10, 1931, several hours after the onset of an attack of coronary occlusion. *Q* wave and high take-off of *R-T* interval in Lead III. Autopsy, 12 hours later, showed fresh thrombus in right coronary artery.

dial disease in cases showing a conspicuous  $Q$  wave in Lead III. That such a relation might exist is suggested by the findings of Pardee<sup>11</sup> in his series of 43 cases. Here there were 16 who did not have the anginal syndrome and of these there was only 1 whose record contained an abnormal  $T$  wave.

Of the 103 patients in the present series, 39 were excluded because of digitalis medication. The remaining 64 were divided into two groups. In the first group were placed the 32 undigitalized patients whose records showed, in addition to a large  $Q_3$ , one or more of the following changes: (1) inversion of (a)  $T_1$  or (b)  $T_2$  and  $T_3$ ; (2) high or low take-off of the  $R$ - $S$ - $T$  interval in Leads I or III; (3) slurring at the apex of  $R_1$  or  $S_1$ . The second group consisted of the remaining 32 undigitalized cases with records showing a deep  $Q_3$  but an otherwise normal  $Q$ - $R$ - $S$ - $T$  complex. As a control series, there were selected 32 undigitalized patients whose records, in the absence of a  $Q$  wave in Lead III, showed the above mentioned changes indicative of myocardial disease.

TABLE 3.—THE RELATIVE INCIDENCE OF CERTAIN CARDIAC SIGNS AND SYMPTOMS IN AN UNDIGITALIZED GROUP OF CASES SHOWING A LARGE  $Q$  WAVE IN LEAD III.

	Group I. $Q_3$ + other ekg. changes.	Group II. $Q_3$ alone.	Control group. No $Q_3$ other ekg. changes as in Group I.
Number of cases . . .	32	32	32
Angina pectoris . . .	23 (72%)	3 (9%)	12 (38%)
Signs and symptoms of acute coronary occlu- sion . . . . .	6 (19%)	0	2 (6%)
Hypertension . . . . .	9 (28%)	6 (19%)	16 (50%)
Absence of cardiac signs or symptoms . . .	0	8 (25%)	2 (?)

NOTE.—Of the 2 cases in the control group listed as being without cardiac signs or symptoms, 1 had syphilis and a possible syphilitic aortitis, while the other was a neurotic woman who showed no cardiovascular abnormalities on physical examination but who gave a history of dyspnea, edema of the ankles and attacks of precordial pain.

The statistics presented in Table 3 suggest that in a group of undigitalized patients, whose records are characterized by a conspicuous  $Q$  wave in Lead III, those cases in which additional evidence of myocardial damage appears in the electrocardiogram may be expected to show a high incidence of angina pectoris. On the other hand, in those instances in which the large  $Q_3$  is the only electrocardiographic abnormality, angina pectoris will be much less frequently encountered and a certain proportion of the cases will be without demonstrable cardiac disease.

**IV. Postmortem Findings.** Of the 103 patients in the present series, 12 came to autopsy (Table 4). On the basis of changes found in the coronary arteries and in the myocardium, the cases were divided into three groups: (1) those showing no significant narrowing of the coronary arteries; (2) those showing narrowing or



occlusion of one or more coronary arteries but no gross infarction of the myocardium; and (3) those showing, in addition to coronary occlusion, a circumscribed area of infarction characterized by gross scarring and thinning of the myocardial wall. In the 4 cases without visible scars, blocks for microscopic study were cut from the anterior apex and the posterior base of the left ventricle. Sections were stained with hematoxylin and eosin and note made as to the presence or absence of perivascular and myocardial scarring.

Three of the 12 cases fell into the first group (Nos. 11853, 12972, 13100). Two of these had a history of hypertension and renal insufficiency. The third was a case of hypertension and polycythemia vera with a terminal miliary tuberculosis. In none was there definite evidence of impairment of the coronary circulation.

In the second group there were 4 cases (Nos. 12024, 12271, 12825, 13056). Three showed marked narrowing of the right coronary artery at some point along its course. The fourth was a case of subacute bacterial endocarditis with a mass of vegetations obstructing the orifice of the left coronary artery. In addition, 2 of the 4 showed marked sclerosis and narrowing of the anterior descending branch of the left coronary artery. There was, however, no evidence of gross myocardial infarction in any of the cases in this group, although in one instance there were many small, linear scars scattered through the myocardium of the interventricular septum.

The third group consisted of 5 cases (Nos. 10745, 10888, 10942, 12802, 13000). In each there was thrombosis of the right coronary artery with infarction of the posterior base of the left ventricle and adjacent portion of the interventricular septum. In two instances the infarct extended to the apex. With the exception of one case, in which a fresh thrombus was considered to be a terminal event, there was no evidence of thrombosis of the anterior descending branch of the left coronary artery or infarction of the area supplied by this vessel.

**V. Mechanism.** Lewis<sup>7</sup> considered that the initial deflection of the *Q-R-S* complex was the result of activation of the interventricular septum and it is on the basis of changes in this region of the heart that most of the theories concerning the origin of the *Q* wave in Lead III arise.

That a significant *Q*<sub>s</sub> may occur in the records of patients without demonstrable coronary disease is evident. The results of the present study do not throw any light upon the origin of this wave in such cases. However, the instability of Lead III has been emphasized.<sup>2</sup> Reference is also made to articles by Ziskin,<sup>17</sup> Edeiken and Wolferth,<sup>3</sup> Meek and Wilson,<sup>8</sup> Purdee<sup>11</sup> and Proger<sup>13</sup> for a discussion of the part played by lateral displacement of the cardiac apex and rotation of the heart around its longitudinal axis in shaping the initial deflection of the *Q-R-S* complex in Lead III.

In contradistinction to the cases without demonstrable coronary

TABLE 4.—POSTMORTEM FINDINGS.

Autopsy No.	Age, yrs.	Sex.	Race.	Angina pectoris.	Hypertension	Interval between ekg. and autopsy.	Heart weight, gm.	Condition of coronary arteries.	Condition of myocardium.
11853	29	F	C	0	+	9 dys.	680	No appreciable sclerosis	Great hypert. of left vent.; no gross visible scarring; micro., a few small perivascular scars.
12972	62	M	W	+	+	2 dys.	610	Moderate sclerosis; no definite narrowing of lumina	Hypert., particularly of left vent.; no scars visible in gross; micro., an occasional perivascular scar in ant. wall of left vent.; focal myocardial scars in mod. number in post. wall of left vent.
13100	65	F	W	0	+	2 yrs., 3 mos., 13 dys.	460	Orifices patent, lumina sclerotic but not greatly narrowed	Marked hypert. of left vent.; rather numerous minute scars scattered throughout myocardium of left vent.
12024	22	F	W	0	0	2 mos., 12 dys.	500	Subao. bacterial endocarditis with aortic insuff. and vegetations on aortic valve; orifice of left artery partially occluded by a mass of vegetations; no coronary sclerosis; in gross, no thrombi seen in any coronary arteries	Mod. card. hypert.; small, grayish scars in myocardium; no gross area of infarct. or thinning of myocardium; micro., many small infected infarcts as result of bits of vegetation plugging
12271	53	M	W	+	+	9 hrs.	400	One branch of ant. descending tion reduced to fibrous cord w out a patent lumen; only sl sclerosis of remainder of left onary; marked sclerosis of right coronary with a fresh thrombus just proximal to post. margin of intervent. septum	vent. or intervent. septum.
12825	68	F	C	+	0	21 dys.	280	Almost complete occlusion, by an atheromatous plaque, of right coronary just at post. margin of intervent. septum; only slight sclerosis of left and remainder of right	A small heart; no areas of infarct.; no scarring of myocardium visible in gross; a roughened patch on endocardial surface of left auricle; micro., a few small and medium-sized fibrous scars in myocardium of left vent.
13056	62	F	W	+	0	11 mos., 20 dys.	380	Distinct narrowing of right orifice by atherosclerosis; patent left orifice but almost complete occlusion of mouth of anterior descending branch by a calcified plaque	Thickened, fibrous epicardium; no visible areas of infarct.; no myocardial scars visible in gross; micro., many small linear scars in wall of left vent. near endocardial surface.
10745	41	M	W	+	0	20 dys.	480	Slight sclerosis of left, extreme of right, with occlusion by a thrombus just proximal to post. margin of septum	Area of infarct., with thinning and scarring of myocardium, at the post. base of left vent. and intervent. septum.
10888	61	M	W	0	+	3 mos., 27 dys.	600	Sclerosis and calcification of both arteries; no great narrowing of lumina except in case of right; thrombosis of right coronary at one point	Hypert. and dil. of both vent.; slight myocardial scarring in ant. wall of left vent.; area of infarct., with gross scarring and thinning of myocardium in post. wall of left vent. and adjacent portion of intervent. septum (Fig. 3).
10942	20	M	W	+	0	1 mo., 8 dys.	720	Aortic insuff. with large, friable vegetations on aortic valve; left coronary orifice patent; no sclerosis or occlusion of left coronary; thrombosis of right artery (embolus?) several cm. proximal to post. margin of septum	Extreme hypert. and dil. of left vent.; large area of infarct. hollowing out muscle in post. wall of left vent. and adjacent portion of intervent. septum; no other visible scars in myocardium.
12802	63	M	W	+	0	5 dys.	400	Sclerosis of both arteries with narrowing of lumina; old, partially canalized thrombus obstructing lumen of right artery just proximal to post. margin of septum; a fresh thrombus present in the already narrowed lumen of ant. descending branch	Many small scars throughout myocardium of left vent.; area of infarct. at post. base of left vent. and intervent. septum.
13000	45	F	C	0	0	16 dys.	520	Syph. aortitis and aortic insuff.; patent left coronary orifice; slight sclerosis of left artery; complete occlusion of right orifice by syph. aortitis and superimposed thrombus; remainder normal.	Infarct. of myocardium at post. base of left vent. and intervent. septum; restriction of affected area to endocardial half of muscle wall.

disease are those with clinical evidence of coronary thrombosis and records which show a deep  $Q_3$  in addition to the changes characteristic of myocardial infarction. In the present series there were 10 such cases. In each instance the large  $Q$  wave was associated with an elevation of the  $R-T$  interval in Lead III or with inverted, "coronary"  $T$  waves in Leads II and III. Six of the 10 patients came to autopsy and, in all but 1, thrombosis of the right coronary artery was found. The exception (No. 13056) showed partial occlusion of both the right and the anterior descending branch of the left coronary arteries but there were no scars visible in the gross. Four of the 6 cases had, in addition, infarction of the posterior base of the left ventricle and adjacent portion of the interventricular septum. In a fifth instance death occurred 6 hours after the clinical onset of the attack. Autopsy (No. 12271) revealed a fresh thrombus in the right coronary artery but no gross evidence of myocardial infarction.

The finding, in cases of coronary thrombosis, of a large  $Q_3$  in association with an elevation of the  $R-T$  interval in Lead III or with inverted, "coronary"  $T$  wave in Leads II and III is in accord with the observations of Parkinson and Bedford.<sup>12</sup> The fact that such curves are characteristic of right coronary artery occlusion was first stated by Barnes and Whitten<sup>1</sup> in 1929. Wilson, Barker, Macleod and Klostermeyer<sup>15</sup> have recently reported similar findings. In addition, Fenichel and Kugell,<sup>4</sup> studying the relation of the large  $Q$  wave in Lead III to myocardial disease, observed infarction or diffuse scarring of the posterior portion of the interventricular septum in a series of 12 cases whose records showed left axis deviation and a conspicuous  $Q_3$ .

It would seem, therefore, that occlusion of the right coronary artery with infarction of the posterior base of the interventricular septum would, in certain cases, constitute an important factor in the production of a large  $Q$  wave in Lead III. Whether or not partial occlusion of the same artery is capable of producing a similar electrocardiographic change seems, at present, uncertain and may depend upon the extent of the collateral circulation. Finally, it is important to consider that in association with coronary disease, the factors which produce a deep  $Q_3$  in cases with normal hearts may be present and complicate the interpretation of the record.

**VI. Summary.** An analysis is made of 103 electrocardiograms characterized by a normal sinus rhythm with a significant  $Q$  wave in Lead III.

A study of the histories of the above cases with reference to the electrocardiographic findings is presented.

The pathologic alterations in the hearts of 12 of the cases are given.

The relation of the  $Q$  wave mechanism to occlusion of the right coronary artery and infarction of the posterior basal portion of the interventricular septum is discussed.

The results of the present study are in accord with the observations of others<sup>3,4,11,14,17</sup> to the effect that the large  $Q$  wave in Lead III, while sometimes present in the absence of heart disease, is frequently associated with serious myocardial damage. Furthermore, it is indicated that when this wave and additional evidence of myocardial disease exist in the record, angina pectoris is often present. Postmortem findings support the view that the deep  $Q_3$  is commonly seen as part of the evidence of the electrocardiographic change occurring after thrombosis of the right coronary artery with subsequent infarction of the posterior base of the left ventricle and adjacent portion of the interventricular septum.

NOTE.—I am deeply indebted to Drs. E. P. Carter and A. R. Rich for their helpful advice and criticism. I also wish to thank Miss J. A. Vickers for her assistance in preparing the photographs of the electrocardiograms. The photograph of the pathologic material was taken by Mr. M. Kough.

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### THE EFFECT UPON THE ELECTROCARDIOGRAMS OF PATIENTS WITH REGULAR SINUS MECHANISM OF QUINIDIN SULPHATE.

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In the routine clinical interpretation of electrocardiograms it is obviously essential to know the effect of various modifying factors, particularly drugs, which change the character of the curves. In

a case of suspected coronary thrombosis, complicated by a paroxysm of tachycardia, the question recently arose as to whether the *T* wave changes were a result of the suspected occlusion or a result of the administration of quinidin sulphate. To clarify this issue, a survey was made of the literature regarding the effect of this drug, and a series of studies were made to substantiate the reported data.

A review of the literature revealed no specific studies of the effects of quinidin sulphate on the electrocardiograms of the patients with normal sinus mechanisms. There was little information regarding the effect of the drug upon any specific mechanisms, other than the studies of Lewis of its action upon the fibrillating auricles. Pardee states in his text that quinidin tends to change the form of the *P* wave, probably by displacing the site of impulse from its normal place in the sinus node. Furthermore, it causes a prolongation of the *Q-R-S* group and a greater prolongation of the *T* wave—evidences of the powerful effect of this drug in delaying the spread of the contraction and the process of the contraction itself. He states also that it produces an abnormal inversion of the *T* wave. According to Pardee, the drug has not received such careful study as digitalis. Lewis makes the general statement that the alkaloid quinidin depresses conduction in all the muscular tissues of the heart, as evidenced by increased *A-V* conduction and widening of the *Q-R-S*. Many authors, such as Jenny, Singer, Frey, Martin, Cheiniesse, Fahrenkamp, and Schott, casually mention the flattening and inversion effect on the *T* wave, widening of the *Q-R-S* and prolongation of the *A-V* conduction.

Summary of the published work would imply that quinidin changes the *T* wave and prolongs *A-V* and intraventricular conduction, with no specific data with reference to dosage or time effects.

The studies made in this report were carried on in a general medical ward of the Cook County Hospital, Chicago. In the first group of cases 10 patients were selected and quinidin sulphate was administered orally in 10-grain doses, 3 times in 24 hours; at 8 A.M., 4 P.M. and 12 midnight. Daily electrocardiograms were taken between 7 and 8 P.M., with 1 or more control electrocardiograms before any drug was given. All other forms of medication were eliminated. Three other cases were selected for study and quinidin sulphate was administered during 2 minutes intravenously in doses of 3 grains dissolved in 20 cc. of distilled water; electrocardiographic tracings were taken from a lead from the chest wall from the 2d and 5th interspaces. Another 3 patients were treated in the same way, except that the regular 3 leads were taken. Another group of 3 patients was given quinidin sulphate, 15 grains, q.i.d., or a total of 60 grains per 24 hours. The data collected from these studies are shown in Charts I, II, III and IV.

**Discussion.** In determining the changes produced in electrocardiograms from any given factor, it is necessary to consider the variations that occur without evident cause. In our experience routine daily curves frequently show minor variations, particularly in the contour of the *P* waves, such as notching and rounding and slight change in heights. The *Q-R-S* may vary slightly in contour, as well as the *R-T* or the *S-T* segment. In diphasic *T* waves it is not uncommon to note mild changes in the character of these waves; therefore, no changes were accepted as evidence of the effect of the drug unless they were consistently present and unless they disappeared on elimination of the drug.

With the dose of 30 to 60 grains per day, which was used as an average amount used therapeutically, no consistent changes were observed in the character of the *P* waves in any lead (Chart I). The *Q-R-S* complexes furthermore showed no appreciable change in time, duration, character or height. The *P-R* intervals remained the same. The only consistent definite deviation was in the effect upon the *T* waves. In 1 case (7.5 per cent) there was a marked flattening; in 2 cases (15 per cent) no appreciable change and in 10 cases (85 per cent) a mild to moderate flattening. The *R-T* or *S-T* segments apparently did not participate in this change as they do in digitalis. It is interesting to note that the greatest change in the character of the *T* waves was in those which were originally high and pointed.

The cases in which no appreciable or minor effects were noted were those in which the *T* wave was either diphasic or low. This evidence of organic change is substantiated by the clinical diagnosis of tabes, terminal endocarditis, malignancy and prolonged *A-V* conduction time. One case had previously received digitalis for several weeks.

The effect of the drug was noted in from 12 to 72 hours, with an average time of 48 hours. The disappearance of the *T* wave deformity was usually in a few days; we were unable to secure information on this point in all the 13 cases. After the *T* wave effect was noted, continued administration of the same dose did not seem to produce any greater effect. The maximal period of observation was 19 days, and in this case the *T* wave became isoelectric in 48 hours and remained so. The characteristic change is shown in Fig. 1.

Chart II shows the data collected when the quinidin sulphate was administered intravenously, and a lead taken directly from the chest wall at the 2d and 5th interspace to the right of the sternum. There were no demonstrable changes in the *P* waves, *P-R* intervals or *Q-R-S* complexes. As a matter of fact, the complexes before and after taking may be superimposed one upon another accurately, so that measurements were not required. The *T* waves only were affected and a small portion of the *R-T* or *S-T* segment.

## MAHER, SULLIVAN, SCHERIBEL: QUINIDIN SULPHATE

CHART I.—EFFECT OF QUINIDIN GIVEN ORALLY (30 GRAINS DAILY).

Case No. and initials.	Diagnosis.	Days of dosage.	Control of EKG. findings.	Changes in EKG. after quinidin.	Time of appearance, hrs.	Time of disappearance.	Remarks.
1. T. Mc.	Arteriosclerosis; hypertension; chronic arthritis	5	P-R int. 0.2 sec.; left axis deviation; Q-R-S slurred in all leads; T waves upright in all leads; P-R int. of 0.26 sec.; left axis deviation; diphasic P in III; T waves upright in all leads	Moderate flattening of T waves in I and II; isoelec. in III	36	6 days	Extrasystole disappeared.
2. J. H.	Duodenal ulcer	8	P-R int. of 0.18 sec.; Q-R-S upslurred R near base line in II and III; T waves all upright in III; diphasic T waves in all leads; notched P in III	Mild flattening of T waves; most marked in II and III	12	Left hospital	None.
3. T. G.	Carcinoma of esophagus	19	P-R int. of 0.16 sec.; Q-R-S notched in all leads; T waves in all leads; notched P in III	Isoelectric T waves in all leads	48	4 days	None.
4. H. J.	Tabes dorsalis	8	P-R int. of 0.16 sec.; Q-R-S diphasic in I and upright in II and III; T wave upright in I, low in II and isoelectric in III	No appreciable change	...	...	None.
5. N. R.	Teratoma of testis with metastases	8	P-R int. of 0.18 sec.; Q-R-S upslurred, upright in I, diphasic in II and diphasic in III	Very mild rounding of peaks of T waves	72	Impossible to determine	None.
6. J. J.	Duodenal ulcer	9	P-R int. of 0.16 sec.; Q-R-S moderately slurred, upright in I and III; T waves upright and broad in I and II and low in III	Moderate flattening of T waves in I and II	36	4 days	None.
7. G. G.	Arteriosclerosis	9	P-R int. of 0.16 sec.; Q-R-S upslurred, upright in I, diphasic in II and low in III	Moderate flattening in all 3 leads	48	4 days	None.
S. J. L.	Ulcerative colitis	8	P-R int. of 0.16 sec.; Q-R-S upslurred, upright in I and II and low in III	Moderate flattening in all 3 leads	48	3 days	None.
9. H. A.	Duodenal ulcer	8	P-R int. of 0.18 sec.; Q-R-S upslurred, upright in I, diphasic in II and low in III	Moderate flattening in all 3 leads	48	Left hospital	None.
10. A. P.	Carcinoma of bowel	6	P-R int. of 0.16 sec.; left axis deviation; Q-R-S notched in III; T waves upright in all leads	Moderate flattening of T waves in all	48	4 days	None.

CHART II.—EFFECT OF QUINIDIN GIVEN INTRAVENOUSLY (3 GRAINS).

Case No. and initials.	Diagnosis.	Control EKG. findings.	Changes in EKG. after quinidin.	Time of appearance.	Time of disappearance.	Remarks.
11. F. H.	Convalescent pneumonia	<i>P-R</i> int. of 0.16 sec.; <i>Q-R-S</i> downward, mildly slurred; <i>T</i> wave broad but pointed	<i>T</i> wave became isoelectric	2 min. from beg. of injection	<i>T</i> wave still flattened after 1 hr. 35 min.	No change in bloodpressure.
12. W. K.	Tuberculosis of cecum	<i>P-R</i> int. of 0.16 sec.; <i>Q-R-S</i> diphasic, mildly slurred; <i>T</i> wave sharply upright	<i>T</i> wave became sharply inverted	<i>T</i> wave isoelectric in 1 min.; 30 sec.; inverted in 2 min.	<i>T</i> wave still flattened in 2 hrs. and 8 min.	No change in bloodpressure.
13. C. F.	Arteriosclerosis	<i>P-R</i> int. of 0.18 sec.; <i>Q-R-S</i> diphasic, mildly slurred; <i>T</i> waves sharply upright	<i>T</i> wave became almost isoelectric	Unknown	Peak of <i>T</i> wave still flattened in 2 hrs. 13 min.	Bloodpressure dropped from 150/60 to 140/60 then 124/60 and back to 144/68.

CHART III.—EFFECT OF QUINIDIN GIVEN INTRAVENOUSLY (3 GRAINS).

Case No. and initials	Diagnosis.	Control EKG. findings.	Changes in EKG. after quinidin.	Time of appearance.	Time of disappearance, hrs.	Remarks.
14. H. L.	Gastric ulcer	<i>P-R</i> int. of 0.16 sec.; <i>Q-R-S</i> upright in all leads; <i>T</i> waves sharp and upright in I and II and flattened in III	<i>T</i> wave markedly flattened in I and II and isoelectric in III	Less than 7 min.	3	Bloodpressure dropped from 155/90 to 135/90.
15. C. C.	Moderate hypertension; arteriosclerosis	<i>P-R</i> int. of 0.18 sec.; <i>Q-R-S</i> upright in I, diphasic in II and III and slightly slurred; <i>T</i> wave pointed and upright in all leads	<i>T</i> waves mildly flattened in all leads	Less than 5 min.	2	Bloodpressure dropped from 140/70 to 125/64.
16. D. J.	Arteriosclerosis; hypertension; cardiac hypertrophy	<i>P-R</i> int. of 0.26 sec.; marked left axis deviation; mild slurring of <i>Q-R-S</i> ; <i>T</i> waves upright and broad in I, isoelectric in II and sharply down in III; vent. premature contr.	<i>T</i> wave in I isoelectric; no change in II; in III <i>T</i> wave became isoelectric	Less than 5 min.	3	Bloodpressure dropped from 152/68 to 130/78; ventricular extrasystoles disappeared.



CHART IV.—EFFECT OF LARGER DOSES OF QUINIDIN GIVEN ORALLY (60 GRAINS DAILY).

Case No. and initials.	Diagnosis.	Days of dosage.	Control EKG. findings.	Changes in EKG. after quinidin.	Time of appearance, hours.	Time of disappearance.
17. F. E.	Chronic colitis	6	$P-R$ int. of 0.14 sec.; mildly slurred $Q-R-S$ ; sinus mech.; $T'$ wave up in all leads			
18. A. R.	Bronchial asthma	13	Sinus mech.; right axis deviation; iso- elect. $T'$ wave in all leads; concave $R-T$ segment	Moderate flattening of $T'$ waves in all leads	24	Unknown.
19. H. G.	Perigastric adhe- sions and gastric ulcer	7	Sinus mech.; $P-R$ int. of 0.18 sec.; $T'$ wave upright in all leads	No change in 13 days; $T'$ wave and $R-T$ seg- ment deformed by digitalis	....	Digitalis taken preced- ing quinidin régime.
				Moderate flattening of $T'$ wave in all leads	48	Unknown.

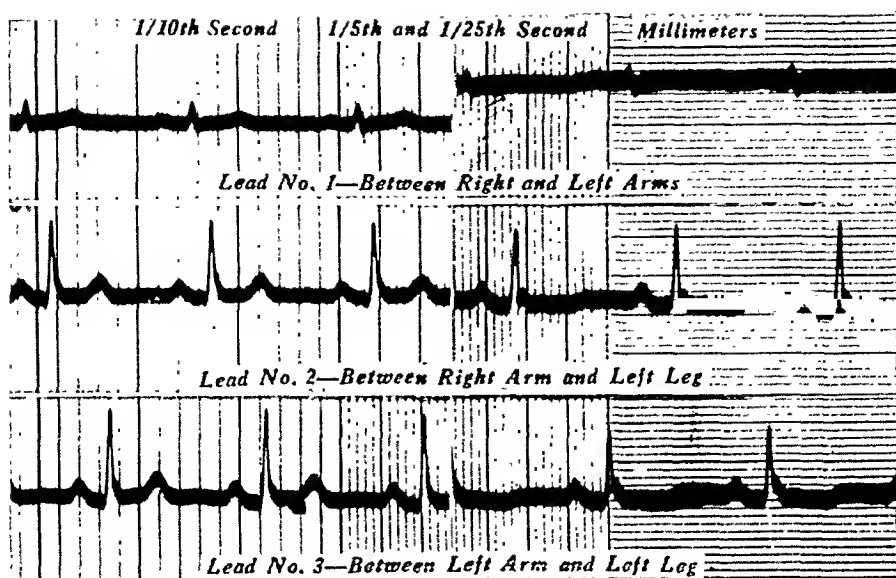


FIG. 1.—Case 3. Normal control electrocardiogram to the left and curve taken after 5 days of oral dosage of 30 grains daily to the right.

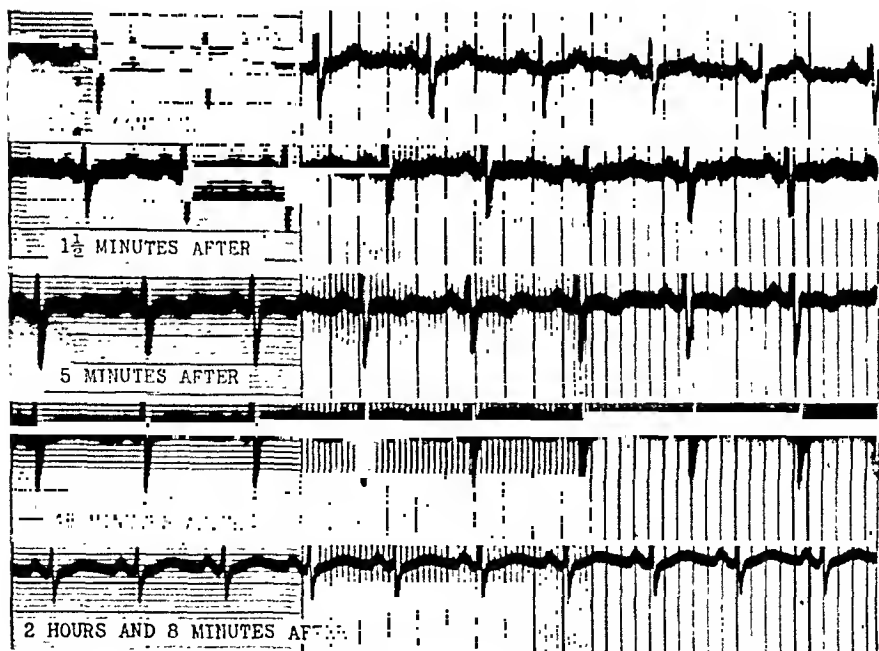


FIG. 2. Case 12. Single chest leads taken after intravenous administration of 3 grains showing gradual change in the contour of the T waves.



This experiment only served to corroborate the findings of the oral administration, namely, that the *T* wave is the primary change. The effect appears in 1 to 2 minutes and wears away in a few hours. No general reactions were noted. The characteristic inversion is shown in Fig. 2.

Chart III shows the effects of the drug in the 3 cases on intravenous administration with the regular 3 leads. Two of these cases, C. C. (15) and O. J. (16), were cardiacs, with organic change. The same phenomenon was noted here: that the change was less than those where the electrocardiograms showed no evidence of defective conduction. The effect disappeared within 3 hours.

In Chart IV the results of the oral administration of 60 grains of quinidin sulphate are shown. The electrocardiographic changes were practically the same as in those who received 30 grains per day. With the higher doses, however, complaints of tinnitus and head noises were noted after the second day. One patient (A. R.) had received digitalis for 3 weeks previous to the administration of the quinidin which produced a deformity of the *R-T* segment and *T* wave in the electrocardiogram. The administration of quinidin caused no change in the contour of this curve.

On the basis of our studies with doses of 30 to 60 grains, administered orally over a period of 5 to 19 days, or intravenous injections of 3 to 5 grains, it would not appear that the findings as reported in the literature of changes in the *P* wave, *P-R* interval, or *Q-R-S* complex were verified. The conclusions of *T* wave changes were amply sustained. In discussion of these discrepancies it is our opinion that changes in the contour of the *P* waves may normally occur in any series of electrocardiograms taken over a period of time. In another series of experiments, yet unpublished, of the effects of quinidin sulphate upon the fibrillating auricle, we have found that when intoxication of the cardiac muscle appears with heavy doses such as intravenous injections of 5 grains every 4 hours for 4 doses, or 10 to 12 grains in 1 injection, in some cases there was a lengthening of the *Q-R-S* complex as well as marked notching and slurring, and the appearance of frequent extrasystoles as well as ventricular tachycardia.

It is our belief that changes of the *Q-R-S* are effects of intoxication by the drug rather than effects that one may expect in therapeutic doses.

**Summary and Conclusions.** 1. Quinidin sulphate was administered to 19 patients, 10 receiving 30 grains orally per day, 3 receiving 60 grains orally per day, and 6, intravenous injections of 3 to 5 grains, with no general toxic effects.

2. The electrocardiograms in the majority of these patients showed changes only in regard to the *T* waves, within 24 to 72 hours if orally administered and immediately if given intravenously.

3. These changes varied from mild flattening to sharp inversion of the *T* waves.
4. The duration of the effect varied from 3 to 6 days on oral administration and 3 hours on intravenous administration.
5. Changes in the *Q-R-S* and *P-R* intervals are presumably effects produced by intoxicating doses.

## THE CLINICAL SIGNIFICANCE OF *B. COLI* HEMOLYTICUS.

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It has been recognized for some time that certain strains of *B. coli* have hemolytic properties, but there is a difference of opinion as to whether they have any definite clinical significance. Their occurrence in humans is chiefly in the gastro-intestinal and urinary tracts.

Schmidt<sup>1</sup> in 1909 described three different types, viz., those producing a clear broad zone of hemolysis on blood (goat) agar plates, those producing a narrower and not entirely clear zone, and a third type in which there was evidence of hemolysis only beneath the colony. Very recently Paulson and Brown<sup>2</sup> have reported that the colony appearance produced by members of the *B. coli* group in blood (rabbit) agar are fundamentally the same as those described by Brown for streptococci ranging from the gamma and viridans non-hemolytic types through the alpha primum and beta hemolytic types.

As regards the frequency of their occurrence in stool specimens, Schmidt<sup>1</sup> concluded that there was no difference between the sick and the well. On the other hand Dudgeon, Wordley and Bawtree<sup>3</sup> found hemolytic *B. coli* in 35 per cent of 21 colitis cases in adults and in 36 per cent of 11 cases of infantile diarrhea, whereas in the stool specimens of 39 normal adults they were recovered in 13 per cent. Todd, quoted by these authors, also found the hemolytic type in 13 instances in stools of 100 infants under 1 year and not suffering from diarrhea. In a later paper Dudgeon,<sup>4</sup> reported that in 200 pathologic cases, typhoid, postdysentery colitis, septic infections of the respiratory tract, hemolytic *B. coli* were present in the feces in 6 per cent and when present at all they completely or almost completely supplanted the non-hemolytic type. Davidson<sup>5</sup> during

a careful bacteriologic examination of stool specimens from 26 normal adults did not find any *B. coli* strains which he considered definitely hemolytic. Meyer and Löwenberg<sup>6</sup> agreed with the finding of Dudgeon, *et al.*, that hemolytic *B. coli* are more frequently present in stool specimens from cases with gastro-intestinal disturbances, as they encountered them in 58 per cent of such cases as contrasted with 25 per cent of normals.

There are few references in the literature to the distribution of hemolytic *B. coli* in the human intestine. Klingenstein<sup>7</sup> made cultures from 42 early postmortems where the intestines were not obviously diseased and in 55 per cent hemolytic *B. coli* were found. Of these cases 9 yielded positive cultures from the jejunum, 14 from the ileum and 19 from the colon. As is well known, the colon group tends to grow at unusually high intestinal levels where there is gastric anacidity, and Adler, Sinek and Reimann<sup>8</sup> have reported that in pernicious anemia cases there may occur large numbers of hemolytic *B. coli* in the stomach and duodenum.

Dudgeon, Wordley and Bawtree<sup>3</sup> in connection with a comprehensive study of urinary infections by the colon group reported that in a series of 91 cases, 76 per cent of the strains isolated from males were hemolytic, whereas in females only 33.7 per cent were of that type. This finding was confirmed by Löwenberg<sup>10</sup> who reported that in a total of 61 cases of pyelitis there occurred 64 per cent infection with hemolytic *B. coli* among the males and 34.6 per cent among the females. Herrold<sup>11</sup> examined 8 selected cases of pyelonephritis with the object of correlating urinary *B. coli* strains with fecal strains. In 5 yielding hemolytic *B. coli*, strains similar by agglutination test with the urine strains were found in the feces or the cervix uteri. He concluded that hemolytic strains have a greater advantage because of virulence than the non-hemolytic but that the latter tend to persist longer. This last suggestion found corroboration in the study of Bitter and Grundel<sup>12</sup> who concluded that hemolytic *B. coli* strains led to a sudden, severe, but short infection of the urinary tract; whereas with the non-hemolytic strains the onset is gradual and the disease tends to become chronic. Of their 92 cases, 32 (34.8 per cent) yielded hemolytic *B. coli*. In an earlier paper<sup>13</sup> however, they reported that 616 pyelitis cases showed only 10.6 per cent with hemolytic *B. coli* but 73.2 per cent of these were females. In a more recent study Hill, *et al.*,<sup>14</sup> found that of 200 Gram-negative bacilli isolated from cases of genito-urinary infection 65.5 per cent were hemolytic.

Tinozzi<sup>9</sup> agreed with Schmidt in considering hemolytic properties of the colon group unrelated to their virulence, for among strongly hemolytic strains one finds those with slight virulence. On the other hand he states that hemolytic strains are more highly agglutinable than the non-hemolytic and the most virulent strains are also the most agglutinable. Dudgeon, *et al.*,<sup>3</sup> have suggested that the

hemolytic variety is especially liable to escape from the intestine into the blood stream whether directly or by way of the lymphatics.

Dudgeon, *et al.*,<sup>3</sup> in their carefully conducted study of the serological relationships among *B. coli* demonstrated that the hemolytic strains exhibit a far greater degree of homogeneity than do the non-hemolytic. They also have greater antigenic (agglutinin producing) properties than the non-hemolytic. This conclusion has received confirmation in the work of Meyer and Löwenberg<sup>6</sup> and of Löwenberg.<sup>10</sup>

In Dudgeon's paper published in 1926, and previously referred to,<sup>4</sup> he states "In my experience, when an abundant growth of hemolytic colon bacilli is obtained from the feces, there is a general toxemia, together with symptoms relevant to the intestinal tract, which may be controlled by specific hemolytic colon bacillary vaccines. This line of treatment in my hands has given better results than I have obtained with vaccine therapy in any other form of intestinal infection. Dudgeon, Wordley and Bawtree have also drawn attention to this fact, and considerable experience has led me to believe that this view is correct. The diarrhea and toxemia may subside, although resistant to other forms of treatment, and certainly vaccine therapy should be employed when these organisms are isolated from the feces and the clinical condition demands it. Patients with this form of intestinal infection may show the presence of specific agglutinins in the blood."

In an experimental study on dogs one of us with Rahe<sup>15</sup> in 1920 reported that it was possible through the use of autogenous vaccines to effect at least a temporary suppression of corresponding strains of *B. coli* naturally vegetating in the intestinal tract. The *B. coli* type employed in the vaccine was an autogenous sucrose-positive strain (*B. coli* communior). Its hemolytic capacity was not tested. A large dosage was used and a coincidence in the rise of the specific agglutinins in the blood with a decrease in numbers of the homologous *B. coli* strain in the stools was noted. As these *B. coli* were merely vegetating in the intestine the result was surprising and seemed to offer a rational basis for attempting to suppress or eliminate by autogenous vaccination more or less definitely parasitized *B. coli* as they occur in the abnormal human gastro-intestinal tract. Since then it has been established to our satisfaction that the same result may be attained with humans. In fact employing a hemolytic type of *B. coli*, which apparently has superior antibody stimulating properties, in the vaccine, a moderate and gradually increased dosage will often within a few weeks effect what is apparently a lasting elimination of that particular strain from the intestinal flora.

Our interest in the clinical significance of *B. coli* hemolyticus began in 1926 and since then we have examined a large number of fecal specimens. It is our purpose to present the results of our

findings, and to record our observations on the effect of treatment with autogenous vaccines, and with diets.

We have recognized as hemolytic *B. coli* only those strains producing a distinct zone of clearing beside the line of surface growth on blood (rabbit) agar. This zone, which may be narrow or broad, is evident within 5 hours' incubation.

The occurrence of *B. coli* hemolyticus in stools was found by one of us (J. C. T.) as in Table 1.

TABLE 1.—THE OCCURRENCE OF *BACILLUS COLI* HEMOLYTICUS.

Type.	No.	Positive.		Negative.	
		No.	Per cent.	No.	Per cent.
Normal adults . . . . .	12	3	25	9	75
Adults with gastric anacidity . . . . .	10	5	50	5	50
Psoriasis in adults . . . . .	30	6	20	24	80
Cases with intestinal disorders, 96:					
Ulcerative colitis . . . . .	41	23	56	18	44
Simple colitis . . . . .	22	13	59	9	41
Intestinal toxemia . . . . .	15	6	40	9	60
Dermatitis (mostly urticaria) . . . . .	11	7	63	4	37
Diarrhea, spastic constipation or flatulence . . . . .	7	7	100		
Totals, 96. Positive, 56 (58.4 per cent); negative, 40 (41.6 per cent)					
Relative numbers of <i>B. coli</i> hemolyticus in positive specimens from among the preceding cases:					
Total cases examined, 46					
With 50 to 100 per cent hemolytic <i>B. coli</i> , 29 (63 per cent)					
With less than 50 per cent hemolytic <i>B. coli</i> , 17 (37 per cent)					

One of us (J. C. T.) has tested the comparative virulence of hemolytic *B. coli* and non-hemolytic *B. coli*. (Table 2.)

TABLE 2.—COMPARATIVE VIRULENCE.

Total strains tested, 102 (85 patients):			
	Total.	Virulent.	Per cent.
Hemolytic <i>B. coli</i> . . . . .	56	30	53.6
Non-hemolytic <i>B. coli</i> . . . . .	46	11	23.9

These strains were isolated from patients exhibiting definite intestinal disabilities or symptoms referred to that tract. The virulence test was made by intraperitoneal inoculation of white mice.

In the laboratory of one of us (W. L. N.) there have been 672 fecal specimens examined from 458 patients. The feces from 161 patients were positive for hemolytic *B. coli*, an incidence of 31 per cent. Dr. Phebe L. DuBois has examined 343 fecal specimens from 219 patients of one of us and two colleagues. She found 161 positive specimens, an incidence of 32 per cent of patients. None of these patients were in normal health and they presented a great variety of diseases.

For the purposes of this study we have taken the clinical records of 180 patients, all private cases, who showed hemolytic *B. coli* in their stools on two or more examinations.



TABLE 3.—PATIENTS SHOWING HEMOLYTIC B. COLI IN STOOLS.

Simple colitis with intestinal toxemia . . . . .	67
Ulcerative colitis . . . . .	6
Urticaria . . . . .	11
Angioneurotic edema . . . . .	5
Acne (simplex and vulgaris) . . . . .	16
Acne rosacea . . . . .	5
Eczema . . . . .	5
Pruritus . . . . .	4
Fibrositis . . . . .	7
Pyelitis . . . . .	5
Chronic infectious arthritis . . . . .	4
Psychoneurosis . . . . .	7
Chronic duodenal obstruction . . . . .	4
Peptic ulcer . . . . .	5
Hypertensive cardiovascular disease . . . . .	9
Epilepsy . . . . .	3
Miscellaneous . . . . .	17
Total . . . . .	180

Of these patient 88 have been treated with autogenous vaccines and the results will be given in subsequent tables. The specific treatment was completed in all previous to March 1, 1932. The results have been ascertained since January 1, 1933, and stools from many have been examined recently.

The method of vaccination has been to give subcutaneous injections of the autogenous vaccine at intervals of 1 week. As many patients are extremely sensitive to the vaccine we begin with very small doses, —0.05 cc. which is equivalent to 50 million organisms, and increase 50 to 100 million according to the absence or presence of reactions. Local reactions are frequent and mild general reactions are not uncommon, while occasionally the local and general reactions are both quite severe. The average maximum dose is 600 million and we have never had occasion to exceed 1,000 million.

Believing that intestinal stasis tends to promote the growth of all organisms, we try to overcome it by mechanical means such as diet, mineral oil and agar. We have, however, seldom observed the disappearance of hemolytic B. coli by such means alone. The fecal specimens have been classified as putrefactive, semiputrefactive or fermentative in accordance with Tsuchiya's<sup>16</sup> classification. About 75 per cent of the stools containing hemolytic B. coli fall in the putrefactive or semiputrefactive groups. We have often been successful in transforming the flora to a fermentative type by diet and sugar but in no instance have the hemolytic B. coli disappeared by this treatment alone. In fact vaccination is the only method which we have found that eliminates the organisms. This has been successful in 93 per cent of our cases and the hemolytic B. coli have recurred in only 3 per cent of our patients whose feces have been re-examined after 1 or more years.

The results of treatment in several groups of patients are shown in Table 4.

TABLE 4.

	No.	Treated with vaccine.	Cured.	Unim- proved.	Remarks.
Simple colitis with intestinal toxemia	67	30	25	0	No hemolytic B. coli in stools within 8 weeks in all but 5; of these, 3 showed very few; 1 recurred after 1 year with return of symptoms; 7 treated with diet, etc., but no vaccine; hemolytic B. coli present in large numbers in all after 4 months or longer.
Ulcerative colitis	6	6	4	1	1 patient apparently cured but relapsed after 1 year with return of hemolytic B. coli in stools; again improved with vaccine.
Urticaria—severe, chronic, recurrent	11	9	9	0	No hemolytic B. coli in stools within 8 weeks in all but 1; no recurrence in 2 years but hemolytic B. coli present in stools.
Angioneurotic edema . . . .	5	5	5	0	All were cured within 12 weeks; none relapsed.
Acne—severe and chronic . . . .	16	14	10	0	All greatly improved but results doubtful as local treatment also was usually given.
Acne rosacea . . .	5	5	5	0	No recurrence.
Eczema . . . .	5	5	5	0	No recurrence.
Pruritus . . . .	4	4	0	4	No improvement in any, but hemolytic B. coli disappeared from stools in all within 12 weeks.
Fibrositis . . . .	7	5	5	0	All had symptoms of intestinal toxemia; no recurrences.
Pyelitis . . . .	5	5	5	0	All had hemolytic B. coli in stools and urine; no symptoms for over 2 years and in none has hemolytic B. coli recurred in stools.

**Summary.** 1. Strains of B. coli possessing hemolytic properties are frequently isolated from human feces (31 to 45 per cent of stools). They are somewhat more often found and in larger numbers in feces from patients with disorders relating to the digestive tract.

2. There is no distinctive difference either as regards morphology or cultural characteristics in the hemolytic B. coli strains isolated from the stools of normal or sick people, although those from the former group have seldom exhibited any virulence.

3. We have been successful in relieving the symptoms of toxemia by autogenous vaccines. B. coli hemolyticus has thus been eliminated from the feces in 93 per cent of our cases. They have recurred in 3 per cent after 1 year or longer.

4. Vaccination is the only method for eliminating B. coli hemolyticus from the human feces which we have found effective.

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## THE FORMATION OF A HEMATOPOIETIC SUBSTANCE IN CONCENTRATED HUMAN GASTRIC JUICE.

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THE therapeutic effectiveness of the parenteral injection of very small amounts of liver extract in the treatment of pernicious anemia was demonstrated by Gänsslen,<sup>1</sup> and Castle and Taylor.<sup>2</sup> Ederle, Kriech, and Gänsslen<sup>3</sup> also showed that an extract of hog gastric mucosa, when injected daily in small amounts, was effective in the treatment of pernicious anemia. Following this work and the fundamental work of Castle and his associates,<sup>4</sup> Morris, *et al.*<sup>5</sup> found that, although small amounts of normal human gastric juice were ineffective when injected intramuscularly, large amounts of normal human gastric juice or hog gastric contents after concentration *in vacuo* produced maximal reticulocyte responses when injected into patients with pernicious anemia. They described the substance in the concentrated gastric juice as being thermolabile, dialyzable, and exhaustible, and therefore concluded that it is probably a hormone. Conner<sup>6</sup> recently reported similar results in one case of pernicious anemia following the injection of normal human gastric juice after vacuum distillation. Wilkinson<sup>7</sup> was unable to confirm

the findings of Morris and his associates when he injected human gastric juice that had been brought to pH 7.5 previous to its concentration *in vacuo*.

In attempting to determine whether it was possible to separate the "active principle" in the gastric juice from the known enzymes (pepsin and rennin) we decided to subject human gastric juice to ultrafiltration. This procedure not only offered a means of determining the relative size of the various constituents of the gastric juice, but also offered a possible method of concentrating the gastric juice at ice-box temperatures.

**Methods.** All of the patients who received the concentrated gastric juice by injection were clinically and hematologically typical of pernicious anemia. Red blood cell counts, hemoglobin determinations (Newcomer), and reticulocyte counts were made daily during the test periods. The gastric juice used was obtained from young, healthy adults following the injection of 0.5 mg. of histamin subcutaneously. Immediately after collection, the gastric juice was filtered through No. 1117½ Falten filter (Carl Schleicher and Schüll). The number of milligrams of pepsin and rennin per cubic centimeter of the gastric juice to be concentrated was determined by methods described previously.<sup>8</sup>

The ultrafilters used in these experiments were of the Bechold type described by Bronfenbrenner.<sup>9</sup> An 8 per cent solution of soluble cotton in glacial acetic acid was deposited under pressure on the inner surface of a Norton alundum thimble. The pressure was applied for 1 minute and the solution was allowed to drain for 3 minutes before hardening.

Since the process of ultrafiltration required approximately 48 hours, the procedure was carried on in the ice box. The vacuum was produced by a water pump capable of reducing the pressure to 15 mm. of mercury. The gastric juice (285 to 630 cc.) was concentrated to a volume of 20 to 30 cc. and then diluted to 200 to 250 cc. with distilled water or 0.3 per cent HCl and reconcentrated to wash out as much of the filterable material as possible. This procedure was carried out twice before the gastric juice was reduced to its final volume of 13 to 15 cc. It was found that only negligible amounts of pepsin and rennin passed through such filters. By determining the amounts of these known enzymes in the ultrafiltrate (the portion of the fluid that passed through the filters), each new filter could be tested for possible defects in its construction.

To test whether the "active principle" of liver extract would pass through this type of ultrafilter, 1 patient with pernicious anemia received intravenously the amount of Liver Extract No. 343 derived from 100 grams of liver after the liver extract had passed through the ultrafilter. The patient's red blood count on the day of injection was 1.6 million, hemoglobin 48.4 per cent, and reticulocytes 0.3 per cent. Five days later a reticulocyte peak of 25.6 per cent (absolute reticulocyte count 620,000 per c.mm.) was reached. This maximal reticulocyte response was followed by marked clinical and hematologic improvement of the patient. This showed conclusively that the active principle in liver extract readily passed through the ultrafilter.

In those experiments in which concentration by vacuum distillation was employed, the procedure was as follows: The distilling flask (fitted with the usual capillary tube to prevent bumping) was immersed in a constant temperature bath maintained at 40° C. The vacuum was produced by a water pump. The gastric juice (500 to 600 cc.) was concentrated to 10 to 15 cc. in a period of from 3 to 5 hours.

**Results.** *I. Normal human gastric juice that had been stored in the ice box for 2 months.* The gastric juice used in the two following tests had been filtered through paper and then stored in the ice box for approximately 2 months. Following this the juice was subjected to ultrafiltration. The data for these experiments can be found in Table 1.

The concentrated juice (that held back by the 8 per cent membrane and which contained the enzymes pepsin and rennin), after being adjusted to pH 7 and passed through an "N" Berkefeld filter and injected into Case 1, produced on two occasions slight but definite reticulocyte rises (8 per cent and 10.2 per cent when the initial red blood counts were 1.38 and 1.60 million, respectively). Slight rises in temperature were the only evidence of reaction following the injections. There was clinical improvement following each injection, but the increases in red blood cells were not sustained and the patient had a further rise in reticulocytes (10.7 per cent) following the administration of Extralin.\* The ultrafiltrate (the portion of the gastric juice passing through the ultrafilter) of this gastric juice was concentrated by vacuum distillation at 40° C., brought to pH 7, and passed through an "N" Berkefeld filter. The juice was then injected into Case 2a (Table 1). There was no reaction, no rise in reticulocytes, and no improvement in the clinical condition of the patient.

The two reticulocyte responses obtained were not maximal; therefore it was assumed that the storage in the ice box had possibly destroyed some of the active material.

*II. Fresh normal human gastric juice.* In this group of experiments the gastric juice was collected as described above, filtered through paper, and immediately ultrafiltered. The properties of the gastric juice, the red blood cell counts, and the hemoglobin and reticulocyte percentages of the patients following the injections are shown in Table 2.

The concentrates of the fresh human gastric juice were injected twice into Case 2 and once into Case 4. No reactions followed the two injections into Case 2 and no response of the blood or improvement in the clinical condition of the patient occurred until the patient received Extralin by mouth. Case 4 had a slight chill and a rise in temperature up to 102° F. following the injection, but there was no improvement in the patient during the 20 days following the injection. A reticulocyte peak of 48.5 per cent then followed the intravenous injection of the amount of liver extract derived from 100 grams of whole liver. Case 3 received the ultrafiltrate of the gastric juice injected into Case 2b after it had been concentrated by vacuum distillation, neutralized, and sterilized by passing through an "N" Berkefeld filter. There was no reaction and no

\* A potent preparation obtained by the interaction of liver or liver extract with hog gastric tissue.

rise in the reticulocytes during the 14 days following the injection. This patient had previously responded to Liver Extract No. 343, but subsequently developed bronchopneumonia and died before again responding to the liver extract. Except for the first injection of the concentrate into Case 2 and the ultrafiltrate injected into Case 3, the materials injected were sterilized by the addition of trieresol. All subsequent preparations were so sterilized.

TABLE 1.—DATA CONCERNING USE OF GASTRIC JUICE STORED IN ICE BOX FOR APPROXIMATELY 2 MONTHS.

Case number	1 (a)			1 (b)			2 (a)		
Cc. gastric juice	350			500			500		
Original juice contained	Pepsin 4.44 mg. Rennin 45 mg.			Pepsin 3.13 mg. Rennin 27 mg.			Pepsin 3.13 mg. Rennin 27 mg.		
Part injected	Concentrate			Concentrate			Ultrafiltrate		
Ultrafiltrate contained	Pepsin 0 Rennin 0.8 mg.			Pepsin 0.02 mg. Rennin 0.12 mg.			Pepsin 0.02 mg. Rennin 0.12 mg.		
Day.	R. B. C. (cc.)	Hgb. (%)*	Retics. (%)	R. B. C. (cc.)	Hgb. (%)	Retics. (%)	R. B. C. (cc.)	Hgb. (%)	Retics. (%)
1	1.38	34.4	0.1	1.60	37.8	1.2	2.06	44.0	0.1
2	1.21	31.3	0.6	1.40	34.4	1.4	1.81	52.1	0.2
3	1.17	29.3	0.3	1.66	37.7	1.1	1.99	49.7	0.1
4	1.40	38.5	0.4	1.59	34.4	1.0	1.85	49.7	0.1
5	1.47	...	0.9	1.36	37.7	2.4	1.45	47.8	0.2
6	1.41	32.7	1.9	1.45	34.4	1.4	1.94	47.8	0.1
7	1.42	36.2	5.6	...	...	2.1	...	...	0.2
8	2.07	38.2	8.0	...	...	4.7	1.99	48.0	0.2
9	1.67	38.2	3.0	1.59	37.0	3.5	2.20	45.8	0.1
10	1.35	35.8	4.0	1.69	37.3	8.8	1.64	44.4	0.0
11	1.58	36.8	2.1	1.42	40.9	10.2	1.55	39.3	0.2
12	...	...	1.2	1.50	39.1	6.3	1.46	35.4	0.3
13	1.60	37.8	1.2	1.65	37.3	4.4	1.43	36.2	0.4
14	...	...	...	...	...	2.3	...	...	...
	...	...	...	1.54	36.2	1.9	...	...	...
Subsequent medication	Extralin 12 capsules daily								
1	1.30	31.5	1.7	...	...	...	...	...	...
3	1.58	36.6	1.1	...	...	...	...	...	...
4	1.70	32.1	2.8	...	...	...	...	...	...
5	1.37	32.1	3.5	...	...	...	...	...	...
6	1.59	39.1	3.5	...	...	...	...	...	...
7	1.59	...	4.3	...	...	...	...	...	...
8	1.45	38.2	5.7	...	...	...	...	...	...
9	1.40	40.4	6.6	...	...	...	...	...	...
10	1.40	40.5	10.7	...	...	...	...	...	...
11	1.67	39.2	7.0	...	...	...	...	...	...
12	1.61	46.7	10.7	...	...	...	...	...	...
13	1.52	50.0	7.3	...	...	...	...	...	...
14	...	...	2.9	...	...	...	...	...	...
	1.81	55.5	3.3	...	...	...	...	...	...
	1.85	53.7	3.7	...	...	...	...	...	...

\* Newcomer method.

The results in this group of observations and those in the preceding group indicated that, although the fresh juice was inactive, the gastric juice that had been stored in the ice box for 2 months contained a demonstrable amount of a substance causing a reticulocytosis when injected into patients with pernicious anemia in relapse. However, Morris and his associates had obtained greater responses of the reticulocytes by the use of similar amounts of

TABLE 2.—DATA CONCERNING USE OF FRESH NORMAL GASTRIC JUICE.

Gastric Juice.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Part injected	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Ultrafiltrate contained	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate	520	Concentrate	285	Concentrate		Retics. (%)
Pepsin 5.7 mg. Rennin 49 mg.	Subsequent medication	Day.	500	Concentrate	500	Ultrafiltrate						

\* Newcomer method

human gastric juice concentrated by vacuum distillation. This indicated that the process of vacuum distillation and, to a less extent, storage in the ice box for 2 months caused some change in the properties of the gastric juice resulting in a hematopoietically active substance.

*III. Normal human gastric juice concentrated by vacuum distillation.* In the first of these tests Case 6 was injected with the gastric juice concentrated by vacuum distillation only. A reticulocyte peak of 11.2 per cent and a satisfactory rise in red blood cells followed the injection. There was no further rise in reticulocytes following the administration of Extralin. In the remainder of the studies in this group the gastric juice was concentrated by vacuum distillation, diluted with distilled water, and then subjected to ultrafiltration. The various preparations were neutralized and then sterilized by the addition of tricresol before being injected into the patients. The properties of the gastric juice and the responses of the blood of the patients are shown in Table 3.

The portions of the gastric juice reconcentrated by the ultrafilters were injected on 4 occasions. A definite reticulocyte response followed each injection. Case 5 had a reticulocyte rise of 9.8 per cent by the 12th day after the injection. The reticulocytes decreased and the patient received Extralin by mouth. A reticulocyte peak of 27.9 per cent was reached 7 days later. The two responses were identical with the responses obtained in Case 11, except that Case 11 received no medication other than the gastric juice injection. Perhaps the second rise in this experiment was due in part to the gastric juice. The reticulocyte peak of 8.7 per cent (red blood cell count 3.25 million) in Case 8 was reached on the 13th day following the injection. There was no subsequent rise in reticulocytes following the intramuscular injection of liver extract. A reticulocyte peak of 8.2 per cent was reached by the 16th day in Case 10. A second reticulocytosis (9 per cent) followed the intramuscular injection of liver extract in this patient. Case 11 also received the reconcentrated gastric juice after he had responded to an injection of the ultrafiltrate. This second injection caused a slight (2.8 per cent) reticulocytosis and a further rise in red blood cells.

The ultrafiltrate of the juice concentrated by vacuum distillation was reconcentrated by vacuum distillation and injected into 2 patients. Case 7, a patient who had had nine previous responses to liver extract administered by mouth or by injection, was in cardiac failure when injected with the concentrated ultrafiltrate. By the 7th day the reticulocytes had started to increase, but the cardiac failure did not respond to therapy and the patient developed a bronchopneumonia and died on that day. Following the injection of the reconcentrated ultrafiltered gastric juice into Case 11 the reticulocytes increased to 8.2 per cent by the 9th day. After decreasing to 2.2 per cent they again increased, reaching 30.6 per cent by



TABLE 3.—DATA CONCERNING USE OF GASTRIC JUICE CONCENTRATED

Case number	6			5			7		
Ce. gastric juice	560			425			560		
Original juice contained	Pepsin 3.9 mg. Rennin 41 mg.			Pepsin 2.9 mg. Rennin 37.5 mg.			Pepsin 2.9 mg. Rennin 37 mg.		
Part injected	All			Concentrate			Ultrafiltrate		
Ultrafiltrate contained	Pepsin — Rennin —			Pepsin — Rennin —			Pepsin — Rennin —		
Day.	R. B. C. (cc.)	Hgb. (%) <sup>*</sup>	Retics. (%)	R. B. C. (cc.)	Hgb. (%)	Retics. (%)	R. B. C. (cc.)	Hgb. (%)	Retics. (%)
1	1.27	....	1.1	0.87	22.2	1.3	1.69	35.1	1.6
2	1.26	29.1	1.6	1.03	19.5	2.0	....	....	1.5
3	1.36	30.1	2.2	0.80	....	1.3	1.39	27.5	1.2
4	1.15	24.9	1.9	0.56	16.0	1.9	1.47	33.4	1.3
5	1.29	26.9	2.6	0.70	....	3.1	1.53	26.2	1.6
6	1.30	29.7	5.0	0.64	17.0	1.6	1.20	22.9	0.6
7	....	....	6.2	0.79	19.5	2.9	1.50	20.7	1.5
8	1.41	30.5	2.6	0.95	18.5	3.1	1.42	20.9	2.3
9	1.50	29.0	5.0	0.84	18.1	5.5	....	....	2.3
10	1.51	31.1	5.7	0.82	19.0	6.7	1.21	24.9	3.1
11	1.05	31.8	11.5	0.70	....	9.8	....	....	....
12	1.76	33.7	10.9	0.72	20.0	6.0	....	....	....
13	1.82	35.8	11.2	0.74	19.7	4.3	....	....	....
14	....	....	7.1	0.85	19.5	3.2	....	....	....
15	1.98	41.4	2.5	....	....	....	....	....	....
16	1.90	45.2	1.1	....	....	....	....	....	....
17	2.10	36.2	3.3	....	....	....	....	....	....
18	2.36	41.0	4.6	....	....	....	....	....	....
19	....	....	....	....	....	....	....	....	....
20	....	....	....	....	....	....	....	....	....
21	....	....	....	....	....	....	....	....	....
22	....	....	....	....	....	....	....	....	....
23	....	....	....	....	....	....	....	....	....
24	....	....	....	....	....	....	....	....	....
25	....	....	....	....	....	....	....	....	....
26	....	....	....	....	....	....	....	....	....
27	....	....	....	....	....	....	....	....	....
28	....	....	....	....	....	....	....	....	....
29	....	....	....	....	....	....	....	....	....
Subsequent medication	Extralain 12 capsules daily			Extralain 12 capsules daily					
1	2.28	44.6	3.4	0.81	18.1	2.4	....	....	....
2	2.24	44.1	2.0	0.76	20.4	4.6	....	....	....
3	2.49	46.2	1.8	0.80	19.9	7.5	....	....	....
4	2.88	54.5	1.0	....	....	7.0	....	....	....
5	2.78	56.4	0.4	0.96	20.9	10.7	....	....	....
6	3.18	59.3	....	0.90	21.0	21.9	....	....	....
7	3.50	56.4	2.2	0.97	22.3	27.6	....	....	....
8	3.48	57.0	0.7	1.25	24.3	27.9	....	....	....
9	3.55	61.4	0.7	1.35	25.3	25.2	....	....	....
10	3.25	58.3	....	1.41	26.0	12.2	....	....	....
11	3.34	57.0	....	....	....	10.6	....	....	....
12	3.66	59.3	0.5	1.59	26.3	7.8	....	....	....
13	3.75	55.5	0.4	1.73	30.5	6.2	....	....	....
14	....	....	....	1.64	31.1	5.4	....	....	....
15	....	....	....	1.84	30.8	4.5	....	....	....

\* Newcomer method.

BY VACUUM DISTILLATION AND THEN ULTRAFILTERED.

8			10			11			11		
560			518			518			630		
Pepsin 2.9 mg. Rennin 37 mg.			Pepsin 2.1 mg. Rennin 32 mg.			Pepsin 2.1 mg. Rennin 32 mg.			Pepsin 2.5 mg. Rennin 39.5 mg.		
Concentrate			Concentrate			Ultrafiltrate			Concentrate		
Pepsin — Rennin —			Pepsin 0 Rennin 0.07 mg.			Pepsin 0 Rennin 0.07 mg.			Pepsin 0 Rennin 0.006 mg.		
R. B. C.	Hgb.	Retics.	R. B. C.	Hgb.	Retics.	R. B. C.	Hgb.	Retics.	R. B. C.	Hgb.	Retics.
(cc.)	(%)	(%)	(cc.)	(%)	(%)	(cc.)	(%)	(%)	(cc.)	(%)	(%)
2.66	72.4	5.1	2.18	50.6	4.5	1.33	31.0	0.7	2.26	41.8	0.3
2.52	62.1	5.9	2.01	46.0	4.3	0.95	27.2	0.8	...	...	2.0
...	...	5.9	1.94	43.0	2.8	1.01	23.0	0.6	2.40	44.6	2.0
2.55	49.9	5.8	1.96	44.1	1.4	0.94	22.4	0.9	2.58	47.8	1.3
2.31	47.8	3.9	2.09	46.2	1.1	1.18	22.4	0.8	2.32	50.6	1.3
2.56	47.1	3.4	1.83	43.0	0.5	0.99	23.4	1.7	2.40	47.1	0.3
2.99	33.0	2.1	...	...	0.8	0.97	...	1.7	2.72	44.2	0.3
2.88	52.1	2.5	2.11	47.1	0.4	0.97	24.9	2.5	2.51	47.8	0.1
3.09	54.5	4.3	1.99	42.5	1.6	1.03	...	3.6	...	...	0.2
...	...	6.6	2.11	50.6	1.2	1.01	22.0	8.2	2.65	47.1	0.1
2.95	55.5	4.9	1.85	49.1	1.5	0.93	26.0	7.1	2.32	47.8	0.5
3.28	59.0	4.9	1.94	47.1	2.2	0.96	24.1	7.0	2.49	42.0	...
2.61	55.5	6.7	1.95	50.5	1.9	1.10	25.2	4.7	2.69	47.1	1.7
...	...	8.7	...	...	1.6	...	...	2.2	2.70	54.7	2.8
3.25	64.9	6.5	...	...	3.1	...	...	4.1	2.44	50.6	0.9
3.21	62.1	6.9	1.60	50.1	4.1	1.22	29.4	3.6	...	...	1.3
...	...	4.8	1.91	...	8.2	0.87	25.2	7.8	3.30	50.6	1.6
3.26	64.9	3.1	2.38	55.5	5.3	0.82	...	10.6	3.28	56.4	0.9
...	...	...	2.39	47.8	4.6	1.18	27.6	13.8	3.04	61.4	1.0
...	...	...	2.66	52.1	3.2	1.46	35.3	20.0	3.24	59.8	...
...	...	...	...	...	3.0	...	...	26.2	3.30	59.3	...
...	...	...	...	...	1.8	1.75	...	30.6	3.44	...	...
...	...	...	2.50	48.4	1.4	1.71	35.4	16.1	...	...	...
...	...	...	2.40	57.0	1.0	1.67	35.0	11.0	...	...	...
...	...	...	2.43	57.0	0.8	2.12	41.6	2.3	...	...	...
...	...	...	2.38	51.3	1.2	2.26	41.8	0.3	...	...	...
...	...	...	2.29	53.5	1.1	...	...	...	...	...	...
...	...	...	...	...	2.6	...	...	...	...	...	...
...	...	...	2.56	44.6	0.8	...	...	...	...	...	...
...	...	...	2.39	48.4	0.9	...	...	...	...	...	...
20 cc. L. E. No. 343 intramuscularly			20 cc. L. E. No. 343 intramuscularly								
3.64	68.1	3.8	2.39	48.4	0.9						
3.33	66.1	3.5	2.20	50.6	1.5						
3.77	66.1	1.0	2.08	47.8	1.3						
3.23	68.8	...	2.05	47.8	1.3						
3.79	62.5	1.7	2.27	53.0	4.0						
3.77	70.2	2.5	...	...	9.4						
...	...	...	2.70	54.5	9.0						
...	...	...	2.69	53.5	6.2						
...	...	...	2.62	59.3	3.2						
...	...	...	2.46	54.5	3.9						
...	...	...	3.14	56.4	...						
...	...	...	3.01	52.1	3.6						

the 21st day. At the onset of the second reticulocytosis there was an increase in nucleated red blood cells, nuclear particles, and myelocytes. In each of the experiments in this group the clinical response of the patient was proportionate to the height of the reticulocyte response. There was some type of reaction following each injection, and the most severe reaction occurred following the injection (Case 11, first injection) which caused the greatest reticulocytosis.

The fact that a definite reticulocyte response followed each injection of the gastric juice concentrated by vacuum distillation corroborated our hypothesis, made at the beginning of this group of observations, that the process of concentration by vacuum distillation produced some changes in the gastric juice. In Group II, however, the ultrafiltrate of fresh normal human gastric juice had been concentrated by vacuum distillation and no hematopoietic activity had been demonstrated in this concentrated juice; therefore it was assumed that the material in the gastric juice that could be made active by vacuum distillation was held back by the ultrafilters. To test this, the next observation was made.

*IV. Fresh normal human gastric juice concentrated by ultrafiltration, diluted with 0.3 per cent hydrochloric acid, and reconcentrated by vacuum distillation.* (See Case 12, Chart I.) Fresh normal human gastric juice (615 cc.) was concentrated by ultrafiltration. The concentrate was washed and then diluted with 0.3 per cent hydrochloric acid to 600 cc. and concentrated by vacuum distillation to 20 cc. The reconcentrated juice was neutralized and sterilized and injected intramuscularly into Case 12. The patient had a severe chill followed by a rise in temperature to 105.8° F. and was ill for 3 days. Within 36 hours the red blood cell count had dropped from 1.52 to 1.09 million, the hemoglobin from 36.2 to 26.5 per cent, and reticulocytes from 3 to 2 per cent, and there was a slight increase in icterus. The reticulocytes reached 10.5 per cent on the 10th day. After decreasing to 4.5 per cent, they again increased. At the beginning of this second rise there was a definite increase of nucleated red blood cells, nuclear particles, and myelocytes. The patient maintained an absolute reticulocyte count between 200,000 and 345,000 for 16 days. After 35 days the red blood cell count was 2.35 million, the hemoglobin 47.8 per cent, and reticulocytes 14.7 per cent. The absolute reticulocyte count on that day was 345,000, which was the peak of the reticulocytosis. By then there had been a definite clinical improvement and a definite increase in the red blood cell count, but the response was not as great as would be expected following the marked reticulocytosis. The patient was still slightly icteric. This response was atypical, as compared with those obtained with liver therapy. A subsequent rise in reticulocytes (15.3 per cent) followed the intramuscular injection of liver extract.

This study showed conclusively that the material in gastric juice which could be made active was held back by the ultrafilters used. It also demonstrated that the gastric juice concentrated by ultrafiltration and reconcentrated by vacuum distillation was hematopoietically active, whereas, on three occasions (Group II), gastric juice concentrated by ultrafiltration only had been inactive. The results obtained in Cases 10 and 11 and those obtained in Case 12 indicated that, after the concentration by vacuum distillation, a goodly percentage of the activity passed through the ultrafilters, although practically all of the material that could be made active by concentration by vacuum distillation was held back by the ultrafilters. It would seem, therefore, that during the process of vacuum distillation a hematopoietically active substance was obtained which was smaller in size than the material from which it was formed, or released.

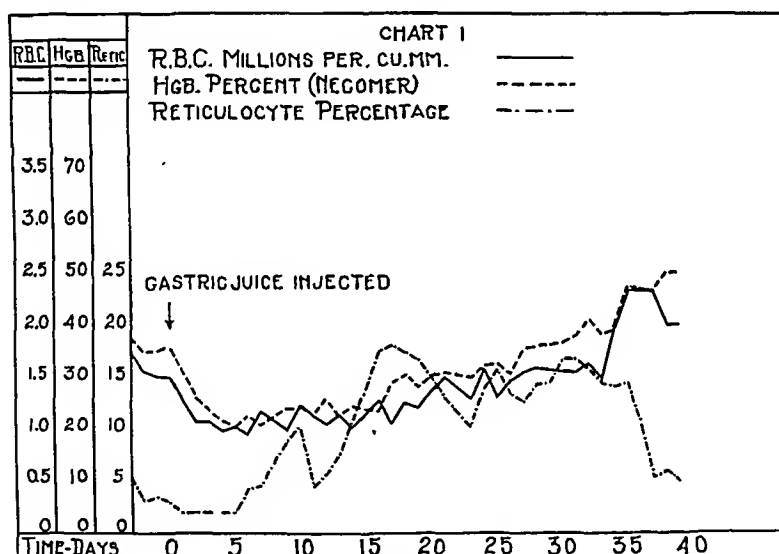


CHART I.

**Discussion.** In attempting to separate the material designated by Morris and his associates as "Addisin" from the known enzymes pepsin and rennin by the process of ultrafiltration, it was found that this could not be done except after concentration by vacuum distillation. Moreover, during the series of observations it became evident that some change in the fresh gastric juice must have taken place before a hematopoietically active material could be demonstrated.

That a change must have taken place was demonstrated when it was found that fresh human gastric juice after concentration by ultrafiltration was inactive; whereas, active preparations were

obtained when gastric juice that had been stored in the ice box for 2 months was concentrated by ultrafiltration and when fresh gastric juice was first concentrated by vacuum distillation. It was more conclusively shown when the concentrate of normal human gastric juice after ultrafiltration—which had been shown to be inactive on 3 occasions—was reconcentrated by vacuum distillation and was found to be quite active. The apparent change in the size of the active material also indicated that some change had taken place.

The actual mechanisms involved in this change are unknown. Three of the possible mechanisms are here presented:

1. *The action of the "intrinsic factor of Castle" upon an extrinsic factor present in the gastric juice.* Castle and his associates have demonstrated the presence of an "intrinsic factor" which when incubated with beef, beef muscle protein and yeast produces a material which will cause reticulocyte responses when fed by mouth to patients with pernicious anemia. It has recently been shown<sup>10</sup> that the incubation of Liver Extract No. 343 with normal human gastric juice markedly increases the potency of the liver extract. This is probably due to the action of the intrinsic factor of the gastric juice upon material in liver extract similar to that in beef muscle and yeast. We now have information, which will be published in detail at a later date, showing that the ultrafiltrate of fresh normal human gastric juice when incubated with Liver Extract No. 343 does not increase the potency of the liver extract, although the portion of the gastric juice concentrated by ultrafiltration does increase its potency. Therefore, it is evident that the portion of the gastric juice which when concentrated by vacuum distillation produces a material hematologically active when injected into patients with pernicious anemia, also contained the intrinsic factor of Castle previous to concentration by vacuum distillation. Moreover, the portion (the ultrafiltrate) which is inactive when concentrated by vacuum distillation does not contain the "intrinsic factor of Castle." The temperature at which vacuum distillation was carried out also offered ample opportunity for the intrinsic factor to act.

It seems reasonable to assume that hog gastric contents contain both the intrinsic and extrinsic factors, because of the presence of gastric juice, desquamated gastric cells, and partially digested food. Therefore the results reported by Morris and his associates, when they injected the concentrated gastric contents of cattle and hogs, could be explained by the action of the intrinsic factor, known to be present, on the extrinsic factor. Although it has been shown that the intrinsic factor is present in human gastric juice produced by histamin stimulation, the presence of the extrinsic factor has not been demonstrated. It is known, however, that gastric juice contains protein substances, and these substances could act as the extrinsic factor. The vitamin B<sub>2</sub> content of human gastric juice

is now being studied. If the extrinsic factor is present in the human gastric juice, some explanation must be made for the failure<sup>4,10</sup> of normal human gastric juice after 4 hours' incubation at 40° C. to produce reticulocyte responses when fed by mouth. At least two reasons suggest themselves. (1) The amount of extrinsic factor is so small that the quantity of the product is inadequate when fed by mouth; (2) in the gastric juice the extrinsic factor is in such a state that more active treatment than incubation at 40° C. is necessary before it can be acted upon by the intrinsic factor. That the intrinsic factor does not act upon the extrinsic factor of the muscle at the site of the injection has been suggested by the fact that the pathologic examination of animals, injected by Morris and his associates and by us, failed to reveal any signs of destruction, and proved by the fact that fresh gastric juice concentrated by ultrafiltration only (containing all the known gastric enzymes and the intrinsic factor) did not produce reticulocyte responses when injected into patients with pernicious anemia.

*2. Production of toxic material which produces the reticulocyte response by bone-marrow damage or by blood destruction.*

Phenylhydrazin, known to destroy red blood cells, is likewise known to produce a long sustained reticulocytosis in patients with polycythemia vera and in animals which receive this medication.<sup>11</sup> As pointed out by Morris and his associates, there is at the time of the reticulocytosis evidence of marked bone-marrow stimulation, that is, increase in nucleated red blood cells, nuclear particles, and myelocytes. Also, the type of the course taken by the reticulocytes is not the same as that seen after liver extract is administered by mouth or by injection. In our experience and in that of Conner, in contrast to the results reported by Morris, the reticulocyte response is delayed. It is also greatly prolonged and sustained, and the rise in red blood cells and hemoglobin percentage is also delayed. This is decidedly not the case when adequate amounts of liver extract are given by mouth or by injection. Delayed responses have, however, been reported when patients received large amounts of gastric tissue by mouth.<sup>12</sup>

In all the studies in which a reticulocyte rise followed the injection of the concentrated gastric juice, the patients had some type of reaction after the injection. The patients who had the greatest reticulocyte responses also had the most severe reactions. However, in some of our studies in which no response of the blood followed the injection, and in the one observation of Wilkinson, the patients experienced more or less severe reactions. Morris and his associates, however, have been able to eliminate the reactions following the injections by means of acetone extraction of the concentrated gastric juice. Even if the reactions are not always associated with reticulocyte rises, the type of reticulocyte response resulting from these injections still suggests that it may be due to bone-marrow irritation

or to actual blood destruction. The fact that concentration by vacuum distillation produces an acidity of the gastric juice approximately equivalent to that of 2 normal hydrochloric acid indicates that considerable hydrolysis, with resulting protein degradation products, might take place. Such protein degradation products could be quite irritating to the bone marrow or could actually be destructive to the red blood cells with the resulting bone-marrow stimulation. Case 12 is of interest in this connection. There was an actual decrease of 0.55 million red blood cells following the injection, and this decrease was accompanied by an increase in icterus. There was no definite increase in the red blood cells of this patient until after a prolonged reticulocytosis. Faber<sup>13</sup> in 1922 reported evidences of bone-marrow stimulation and occasionally rises in red blood cells and hemoglobin following the injection of sterilized milk into patients with pernicious anemia. The responses did not always follow the injections, however. No reticulocyte counts were recorded.

3. *Activation of a gastric hormone.* If the substance in normal human gastric juice, concentrated by vacuum distillation, which produces reticulocyte responses when injected into patients with pernicious anemia, is a hormone, our work demonstrates that the hormone must be activated by concentration by vacuum distillation, or by standing in the ice box for at least 2 months before it will produce a reticulocytosis. The results of our studies confirm the findings of Morris and his associates with regard to the fact that a hematopoietically active substance can be demonstrated in gastric juice concentrated by vacuum distillation when injected into patients with pernicious anemia in relapse. The prolonged reticulocytosis and the evidence of marked bone-marrow stimulation were likewise observed by us. However, we were unable to demonstrate the presence of a hematopoietically active material in human gastric juice until some change in the gastric juice had occurred. It is our opinion, therefore, that the hematopoietic substance must be formed by the action of the intrinsic factor on an extrinsic factor, or by the production of a substance irritating or toxic to the hematopoietic system.

**Summary.** 1. By the methods employed it was found impossible to separate the enzymes, pepsin and rennin, from the hematopoietic substance in human gastric juice except after concentration of the gastric juice by vacuum distillation.

2. The process of concentration by vacuum distillation or storage in the ice box for 2 months was necessary before the presence of a substance capable of producing a reticulocyte response when injected into patients with pernicious anemia could be demonstrated.

3. The possible mechanisms involved in this change in the gastric juice have been presented.

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## STUDIES ON THE PHYSIOLOGY OF THE PARATHYROID GLANDS. IV. RENAL COMPLICATIONS OF HYPER-PARATHYROIDISM.

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SIMPLE hyperparathyroidism is now a well understood disease. Its cardinal metabolic abnormalities are hypercalcemia, hypophosphatemia, hypercalciuria and hyperphosphaturia. Its usual clinical import centers around the symptoms arising from the accompanying skeletal decalcification and dephosphatization. The present paper is concerned with the types of renal complication which may be associated with hyperparathyroidism, and the case history and metabolic findings in a patient with one of these types are set on record.

It is probable that the kidney may be involved in hyperparathyroidism in three entirely different ways, here referred to as Types I, II and III. These are arranged in order of the severity of the hyperparathyroidism with which they are apt to be associated. It



will be easier to discuss Type III before Type II. The essential features of the types are as follows:

*Type I.* Pyelonephritis secondary to formation of calcium phosphate stones in renal pelvises.

*Type III.* Acute parathyroid poisoning with anuria, and death from undetermined cause in a few days, with calcium deposits in kidney parenchyma as well as in other organs, but with no chronic renal changes.

*Type II.* A condition midway between these two, which simulates both chronic glomerular and vascular nephritis. It differs from Type I in that the deposits are in the kidney parenchyma rather than in the kidney pelvises, and from Type III in that the kidneys show long-standing changes and may be the only organs involved in the calcium deposits.

*Type I Variety of Renal Involvement in Hyperparathyroidism.* The formation of renal calculi in hyperparathyroidism with resulting pyelitis and pyelonephritis has been so much emphasized by all writers on the subject that it requires little discussion. The sequence of events is very simple. The calcium and phosphorus excretions in the urine are much increased in this disease; this predisposes to the formation of stones; the subsequent course is that of recurring renal stones. Among the first case reports of renal calculi in typical hyperparathyroidism were the 2 cases reported by Stenholm in 1924.<sup>1</sup> In both instances the stones were bilateral. Mandl's original case,<sup>2</sup> the first one diagnosed as hyperparathyroidism, excreted a white sediment in his urine as did the first patient, C. M., studied in this clinic,<sup>3</sup> although neither showed renal calculi by Roentgen ray. C. M., however, subsequently did show renal calculi as well as evidence of Type II renal involvement (*v. infra*). Other cases to show renal calculi were those of Harbitz, 1915;<sup>4</sup> Hoffheinz, 1925;<sup>5</sup> Wanke, 1926;<sup>6</sup> Parreira and Castro-Freire, 1926;<sup>7</sup> Barr, Bulger and Dixon, 1929;<sup>8</sup> Leri, *et al.*, 1930;<sup>9</sup> Hunter, 1931;<sup>10</sup> Cosin, 1931;<sup>11</sup> Weil, *et al.*, 1931;<sup>12</sup> Hunter, 1931—3 additional cases;<sup>13</sup> Fraser, 1931—3 cases (quoted by Hunter<sup>13</sup>); Albright, Bauer, Claffin and Cockrill, 1932;<sup>14\*</sup> Noble, 1932,<sup>15</sup> and 3 unpublished cases from this clinic. Thus actual renal stones occurred in 23 proven cases. This is an incidence of 27 per cent in the series of cases which the writers have analyzed. This series included 74 cases from the literature, 7 unreported cases from this clinic, an unreported case from the Johns Hopkins Hospital Clinic, and a new case reported in this paper, making a total of 83 cases, 10 of whom have been studied in this clinic. This series does not include cases with histologic or chemical evidence of hyperparathyroidism when the tumor has not been found, nor cases with a parathyroid tumor but no histologic or chemical evidence of hyperparathyroidism. Renal stones should

\* At the time this patient was reported no parathyroid adenoma had been found, but a subsequent operation revealed the tumor.

always bring up the question of an underlying hyperparathyroidism. The Urologic Service at this hospital recently has been doing routine serum calcium and phosphorus determinations on patients with renal stones, and at the time of writing has made the diagnosis of hyperparathyroidism 4 times where the diagnosis would never have been suspected otherwise. Only 2 of these have yet come to operation and in each patient a parathyroid adenoma was found.

*Type III Variety of Renal Involvement in Hyperparathyroidism.* Collip<sup>16</sup> showed that excessive doses of parathormone in dogs resulted in a few days in death, which was preceded by anuria and retention of nitrogenous products. Hueper<sup>17</sup> showed that such dogs dying from acute parathyroid poisoning, as it were, had calcium deposits in their thyroid glands, mucous membrane of the stomach, lungs and kidneys. There seems little doubt, therefore, that an excessive level of the parathyroid hormone in the blood in a few days can so alter the equilibrium that calcium in some form is deposited into the tissues mentioned and death ensues. The kidney lesions here are only a part of a more generalized process. The term "Type III variety of renal involvement" is used to designate the type of lesion seen in parathyroid poisoning.

From a clinical point of view the chief importance of this condition is its avoidance while parathormone is being used therapeutically. No instance of acute parathyroid poisoning from injection of the hormone has been reported. Many of the cases of hyperparathyroidism reported in the literature, however, are at about the critical level where one might expect the complication of parathyroid poisoning. It would be surprising if some did not transgress the level. It seems most likely that the patient reported by Dawson and Struthers<sup>18</sup> is a unique instance of acute parathyroid poisoning occurring in man due to a parathyroid tumor.

The patient, a 49-year-old laborer who, for several years, had had symptoms referable to his skeleton, "on the 24th of October was suddenly seized with a heart attack and was admitted to the hospital in the evening in a state of collapse with a very rapid and feeble pulse. He was too ill to give an account of himself and died suddenly the following morning without any precise conclusion as to the cause of the collapse having been arrived at." Autopsy revealed osteitis fibrosa cystica generalisata of von Recklinghausen. Except for the skull and humerus the disease was in an early stage. A parathyroid adenoma 1 inch in length was found. The internal organs showed no macroscopic changes. Microscopically, calcium deposits in the form of fine granules, which in some instances became confluent masses, were present in all the internal organs. Special sites of deposits were the internal elastic lamina of the arteries, heart wall, lungs, stomach and kidneys.

There seems almost no question but that this patient was suffering from hyperparathyroidism complicated by parathyroid poisoning

which caused a "chemical death." It would appear, therefore, that a condition analogous to parathyroid poisoning in dogs may occasionally occur in man. It must be emphasized that it is rare and that the diagnosis should be confined to cases showing a rapid exit—chemical death, as it were—calcium deposits in multiple tissues at postmortem, and absence of chronic changes in the kidneys.

*Type II Variety of Renal Involvement in Hyperparathyroidism.* There are many cases of hyperparathyroidism with renal lesions on record which do not fall into either Type I or Type III groups. In Type I it would appear that calculi are precipitated out from the urine as secreted by the kidney, thus forming stones in the kidney pelvis; in Type III the supposition is that calcium phosphate is precipitated out from the intercellular fluid into multiple organs, including the kidney; in Type II the evidence, we believe, suggests that the calcium phosphate is precipitated out of fluid in the tubules, forming concretions in the kidneys which eventually lead to inflammatory changes, sclerosis and contracted kidneys.

Of our series of 83 cases, 17 taken from the literature show evidence of chronic parenchymatous kidney pathology. This high incidence shows that there must be some causal relationship. The descriptions of the kidneys in the individual cases seem consistent with the sequence of events suggested above. These descriptions are given below (*q. v.*).

We had the opportunity to study recently a patient who has typical Type II renal involvement, and the metabolic studies threw further light on this condition.

**Case Abstract.** Patient C. E. S. (M. G. H. No. 320037), a white girl, aged 13, entered this hospital on March 17, 1932, having been referred by Dr. A. S. Merrill of Manchester, N. H., because of the following findings. She is the youngest patient with bone trouble in our series, there being only 3 other cases under 20 years (Cosin,<sup>19</sup> aged 17; Cooley,<sup>20</sup> aged 14, and Pemberton and Geddie,<sup>21</sup> aged 14). Her chief complaint was bone trouble of 2 years' duration. Her first symptom was a slight limp in the left leg associated with slight stiffness of the left knee. This knee gradually began to rotate inward a little, and 1.5 years before admission was operated upon for a cyst and a portion of the bone was removed. Five months before entry the right knee began to catch when she stepped on it in a certain way, causing sharp pains, but never preventing her from fully extending her leg. Otherwise the child was able to be up and about and to play a little with other children. Her appetite was good although she had lost 6 pounds during the previous 6 months. During the past 3 to 4 years she had been troubled with enuresis and nocturia (2-3 $\times$ ). She urinated 6 to 10 times during the day and drank 12 and 13 glasses of water. On a fixed water intake of 2000 cc. on the ward she was constantly thirsty. Her dietary history was not remarkable.

*Past History.* She had an unexplained rash at 18 months, whooping cough at 8 years, measles at 11, and only 2 or 3 "sore throats" during her entire life. Her tonsils and adenoids were removed at 7 years. She sustained a fracture of the right forearm at 9 years, as a result of adequate trauma. Catamenia began at 11 years.

*Physical Examination.* A rather flabby, pale, little girl, normally developed for her age, and very intelligent. Her gait had a peculiar wobbling character, suggesting relaxation of joint ligaments together with marked hypotonia. There was a valgus deformity of the right knee. At least 20 purpuric spots up to 2.5 cm. in diameter were present on her extremities. The retinal arteries showed rather marked variation in caliber. The blood pressure was 150/80. The heart was enlarged to the left, 1 cm. beyond the midclavicular line. The apex impulse was forceful and there was an apical systolic murmur.

*Laboratory Examinations.* Urine: Specific gravity during a concentration test varied only between 1.002 and 1.005; albumin, strongly positive; sediment, many white cells without casts. Red count, 4,300,000; hemoglobin, 80 per cent; white count, 8900. Blood smear normal except for slight achromia; Hinton test, negative; basal metabolism, +4; phenol-sulphonaphthalein intravenous renal function test, 15 minutes, 1 per cent excretion; 30 minutes, 4 per cent excretion; 90 minutes, 10 per cent excretion. Blood non-protein nitrogen, 55 and 66 mg. per 100 cc.; serum carbon dioxid combining-power, 44.4 volumes per cent; serum protein, 6.5 per cent; serum calcium, 12 mg. per 100 cc.; serum inorganic phosphorus, 4.7 mg. per 100 cc; plasma phosphatase, 36 units (method of Bodansky<sup>22</sup> where normal is about 3 units).

*Roentgen Rays.* "All the vertebræ of the spine show a distinct variation from the normal. Changes are most marked in the lumbar and lower dorsal region and consist of a disturbance of normal trabeculæ. Denser areas are just below the intervertebral disks, midportions of the vertebræ being more radiant." "The long bones, skull, and pelvis are also grossly abnormal. Most marked changes are at the epiphyses where almost complete decalcification or acalcification is present and considerable interference in growth has taken place. Decalcification extends, however, to involve the shafts and flat bones. There are changes suggesting partial displacement of epiphyses and periosteal reaction. The skull and pelvis present finely granular appearance with some increase in width in bone and miliary areas of decalcification and increased calcium deposit. Bones of the pelvis show what appear to be definite cystic areas. No other cystic areas are seen in any of the long bones. The ribs on the left side, left femur, and distal epiphyses of radius and ulna show a marked deformity. The appearance in the skull and pelvis is almost identical with osteitis fibrosis cystica and hyperparathyroidism. Changes in the epiphyses, periosteum and vertebræ are rather unusual." (Drs. G. W. Holmes and A. O. Hampton.)

*Diagnosis.* The polyuria, polydipsia, decalcification with cyst formation, and hypercalcinemia seemed consistent with hyperparathyroidism. The absence of hypophosphatemia was against this diagnosis, but it was thought that this might be ascribed to the renal involvement. Renal insufficiency there was in any event, but the question was whether this was secondary to a hyperparathyroidism or whether the renal condition was primary and the skeletal changes represented renal rickets, the exact nature of which is still somewhat problematical (*v. infra*). Metabolic studies were made, but were not helpful in making a diagnosis, since they were not typical of uncomplicated hyperparathyroidism. This lack of confirming evidence of hyperparathyroidism we had to discount, however, in view of the renal impairment, the modifying effect of which on the metabolic findings in hyperparathyroidism had never been studied. It was decided that the only hope rested on the diagnosis being hyperparathyroidism, and the patient was explored. A biopsy on the right iliac crest was first performed, however, to rule out multiple myeloma. A parathyroid tumor (22 by 17 by 10 mm.) was found on operation and removed.

*Biopsy Report.* Osteitis fibrosa cystica.

*Pathologic Report.* The gland is typical parathyroid tissue. The cells with the exception of one circumscribed area are the rose-red type of chief cell. There is, however, a circumscribed area, not separated from the rest of the gland by any connective tissue septum, in which the cells are larger and lighter (see "plant-cell-like chief cell," see also "Wucherungsherde," Erdheim<sup>23</sup>). Welch cells are absent. No colloid is seen. There is a lace-work structure of connective tissue which divides the whole gland into small acini.

*Course in Hospital.* The evening of the operation (April 9) she developed tingling in the fingers, and by the next morning she had a positive Chvostek sign. On April 12 she developed mild carpopedal spasm and a positive Trousseau sign (serum calcium = 7.5 mg. per 100 cc.). She was discharged from the hospital on June 16, 1932. At that time there had been no demon-

TABLE 1.—METABOLIC DATA ON K. S. BEFORE AND AFTER REMOVAL OF PARATHYROID TUMOR.

Metabolic period.	Urine, cc.	Calcium, gm.				Phosphorus, gm.				Serum, mg. per 100 cc.		Plasma phosphatase, units.	Remarks.
		Urine.	Feces.	Intake.	Balance.	Urine.	Feces.	Intake.	Balance.	Ca.	P.		
I	4520	0.29	0.06	0.31	-0.94	1.18	0.96	1.74	-0.40	13.6 (II)*	4.3	36	Enuresis.
II	6000	0.27	0.64	0.31	-0.60	1.55	1.21	1.74	-1.02	13.6 (II)	4.2	..	Enuresis.
III	5920	0.29	0.64	0.31	-0.62	1.40	0.53	1.74	-0.19	12.6 (I)	4.4	37	Enuresis.
Blank 3-day period..	...	...	...	...	.....	...	...	...	.....	10.4 (I) 8.3 (II) 7.5 (III)	4.2 3.3 4.1	38	Operation (I).
Blank 3-day period	...	...	...	...	.....	...	...	...	.....	7.7 (I) 6.1 (II) 5.7 (III)	4.3 4.4 4.7		
Blank 3-day period	...	...	...	...	.....	...	...	...	.....	7.5 (I)	4.7		
Blank 3-day period	...	...	...	...	.....	...	...	...	.....	5.3 (I) 5.5 (III)	5.0 5.3		
IV	5945	0.08	0.48	0.28	-0.28	1.18	0.50	1.56	-0.12	6.5 (I)	6.4	..	Enuresis.
V	5710	0.06	0.32	0.31	-0.07	1.14	0.50	1.73	+0.09	6.0 (III)	6.2	..	Enuresis.
VI	5700	0.07	0.37	0.31	-0.13	1.14	0.62	1.74	-0.02	....	..	..	Enuresis.
VII	5860	0.08	0.47	0.31	-0.24	1.10	0.77	1.74	-0.13	8.0 (III)	6.4		
VIII	5760	0.10	0.19	0.31	+0.02	1.02	0.21	1.74	+0.51	7.6 (III)	5.7		
IX	5390	0.08	0.57	0.31	-0.34	0.90	1.00	1.74	-0.16	....	..	15 (III)	
X	5680	0.09	0.41	0.31	-0.19	0.90	0.80	1.74	+0.04				
XI	5530	0.08	0.59	0.31	-0.36	0.88	0.72	1.74	+0.14	8.0 (III)	5.7	19 (III)	

\* Roman numerals indicate to which day of period—1st, 2d, 3d—notation refers.

strable change in her urinary findings, kidney function, or bone Roentgen rays. Her postoperative course was complicated only by a few episodes of vomiting and by mild attacks of carpopedal spasm, for which parathormone was administered on 4 occasions and calcium gluconate on 4 occasions.

*Metabolic Findings.* The metabolic data are contained in Table 1. They consist of calcium and phosphorus determinations on the urine and feces

during 16 3-day metabolic periods. The methods were those previously employed in this clinic.<sup>24,25</sup> Periods 1 to 3 were pre-operative; periods 4 to 11 were postoperative. Sufficient time (about 6 weeks) elapsed between periods 3 and 4 to allow the patient to recover from the immediate effects of the operation. The patient was on a neutral low-calcium diet during the entire experiment.

The calcium excretion in the urine during periods 1 to 3 is quite interesting. It averaged 283 mg. per 3-day period. This figure is to be compared with 190 mg., the average urinary calcium excretion for normal individuals on a similar régime,<sup>26</sup> and 1310 mg., the corresponding excretion of a patient with a hyperparathyroidism and a blood calcium of about 14 mg.<sup>3</sup> It will be seen that the high urinary calcium excretion usually seen in hyperparathyroidism is apparently much reduced in the presence of this renal complication. The average fecal calcium excretion per 3-day period was 744 mg., which is slightly higher than the figure of 600 mg. obtained for normals. The significance of this is increased by the fact that in hyperparathyroidism as a rule there is a decreased amount of calcium in the feces (see Albright, Bauer, Claffin, and Cockrill,<sup>14</sup> observation VII, p. 421). The net result was an average negative calcium balance of 722 mg. per period as compared with 460 mg. for the normals. In brief, this patient excreted less calcium in the urine and more in the feces than would have been predicted had she not had renal disease complicating the hyperparathyroidism. An examination of the phosphorus figures during periods 1 to 3 reveals very much the same thing. There was an average negative phosphorus balance of 537 mg. during these periods, but whereas in simple hyperparathyroidism the phosphorus excretion is almost entirely in the urine,<sup>14</sup> here 40 per cent of the excretion was in the feces. It seems apparent that the lack of hypophosphatemia in this patient was connected with this relative lack of phosphorus excretion by the kidney.

The findings during periods 4 to 11 are about what one would expect. The urinary calcium excretion was below that of normal, but not less than what one would expect for the degree of hypoparathyroidism present (serum calcium, 6 to 8 mg.); the fecal calcium excretion was about normal, which further emphasized the observation that it was increased during periods 1 to 3; the urinary phosphorus excretion in spite of the higher serum phosphorus was much reduced from the pre-operative figures with less reduction in the fecal phosphorus excretion, the ratio of fecal phosphorus to total remaining about 40 per cent (actually 38+ per cent).

The plasma phosphatase findings were interesting. They were very high and apparently stationary before the operation (36 units per 100 cc. 23 days before the operation and 37 units on the day of the operation). Two days after the operation the level was 38 units; 23 days after, the level had fallen to 24 units. The fall continued, and after 54 days a value of 19 units was obtained; 3 days later a value of 15 units; and 1 week later (64 days after operation) a value of 19 units. The normal value by the method employed<sup>22</sup> is about 3 units. These findings show pretty clearly that the hormone is not directly concerned in the production of the enzyme, but rather produces bone changes which in turn are associated with an enzyme increase. Normal enzyme levels are not to be expected until the bone changes have entirely regressed.

From the metabolic data the following conclusions are suggested:

I. Renal insufficiency complicating hyperparathyroidism may produce: (a) An absence of the characteristic finding of hypophosphatemia; (b) a reduction of the characteristic high partition of phosphorus excretion in the urine as compared with the feces, and

(c) a reduction of the characteristic hypercalcaemia and an increase of the characteristic decreased fecal calcium excretion.

II. The level of plasma phosphatase is not directly related to the parathyroid hormone, but is dependent on the bone changes.

*Metabolic Studies, on Previously Reported Case, Before and After Development of Renal Impairment.\** The above observations are substantiated by similar studies on another patient. This second patient was the same sea captain, C. M., who had already been the subject of several investigations.<sup>41,25,27,3,28</sup> His story to this time was one of typical hyperparathyroidism in 1926; removal of 2 parathyroid glands which were normal or even hypoplastic in appearance; no subsequent change in his calcium and phosphorus metabolism (in spite of many quotations to the contrary in the literature); improvement with dietary measures; but renal impairment (Types I and II) during the past year. In spite of several attempts, no more parathyroid tissue had been found.† He was studied for 4 3-day periods on a low-calcium neutral diet, and it is of interest to compare these data with similar data obtained in 1926 before the development of the renal impairment. The average figures are shown in Table II. It will be observed that the observations noted above are substantiated.

In June, 1932, the following laboratory data of interest were obtained. The Roentgen ray of the kidneys showed, besides stones in the pelvis, "probable calcification in the region of the cortex of the right kidney" (Dr. A. O. Hampton). The urinary findings were albumin, moderately positive; sediment, many white blood cells with rare hyalin and granular casts. The blood non-protein nitrogen was 58 mg. per 100 cc.; the carbon dioxide combining-power of whole blood was 48.6 volumes per cent. Three months later the phenolsulphonephthalein excretion was 10 per cent in 2 hours after intramuscular injection.

**Reported Cases of Hyperparathyroidism with Renal Lesions.** I. *Askanazy*.<sup>36</sup> Interestingly enough this is the first case of hyperparathyroidism on record (1903). Abstract from autopsy: "Both kidneys are removable only with difficulty from their capsula fibrosa; are small and fairly soft; and have surfaces which are definitely granular. On the cut surface one sees homogeneous pale-red tissue with white calcium streaks in the pyramids."‡ Microscopically "the kidneys show the picture of interstitial nephritis with many small areas of calcification in the cortex and medulla."

II. *Molineux*.<sup>37</sup> Case 2. Woman, aged 59, with "contracted kidneys."

III. *Idem*. Case 3. Woman, aged 48, with "contracted kidneys."

IV. *Harbitz*.<sup>4</sup> Autopsy diagnosis: "Chronic interstitial nephritis, associated with pyelitis and calcareous concretion of phosphates and carbonates."

\* The new metabolic data on this patient were furnished us by Dr. Walter Bauer, to whom we are much indebted.

† At a 7th operation a parathyroid tumor was removed from the anterior mediastinum. Death ensued several weeks later due to a complication.

‡ Translations are our own.

V. *Meyer*.<sup>38</sup> Microscopic findings. "In the cortex one sees many hyalinized degenerated glomeruli. Besides the fully hyalinized glomeruli one sees some with a concentric connective tissue capsule of a thickness varying up to total replacement of the glomerulus. The epithelium of the tubuli contorti for the most part is well stained. Here and there one finds, however, tubules with desquamated epithelium without nuclei. Fat is not demonstrable in the epithelium. The lumina of the tubules is often noticeably wide. There are no demonstrable changes in the vessel walls. Nevertheless, one finds in the vicinity of small vessels many fresh hemorrhages. Blood cells are often present in the lumina of the tubules. The connective tissue shows, especially in the region of more or less severely altered glomeruli, a marked degree of infiltration with round cells. In the middle of such infiltrations one sees flaky calcium concretions stained blue-black. Here and there it can be clearly seen that these calcium concretions are deposited on the tubular epithelium. In the medulla there are many calcium deposits also, sometimes surrounded by an area of inflammation, sometimes lying in the lumen of a tubule and causing no reaction. In the neighborhood of such calcium infarcts one sees many markedly dilated urinary tubules. Besides the inflammatory infiltration one finds, in the medulla as well as in the cortex, areas of fibrous connective tissue with few nuclei."

TABLE 2.—A COMPARISON OF THE CALCIUM AND PHOSPHORUS METABOLISM OF A PATIENT WITH HYPERPARATHYROIDISM BEFORE AND AFTER DEVELOPMENT OF RENAL IMPAIRMENT. THE FIGURES FOR NORMAL INDIVIDUALS ARE LIKEWISE INCLUDED FOR COMPARISON.

	Calcium, gm.					Phosphorus, gm.					Serum, mg. per 100 cc.	
	Output.			Intake.	Balance.	Output.			Intake.	Balance.	Ca.	P.
	Urine.	Feces.	Total.			Urine.	Feces.	Total.				
Control series† . . . . .	0.13	0.32	0.45	0.33	-0.12	1.21	0.60	1.81	2.07	+0.26	10.0*	4.0
Average of 3 periods in 1926 before renal impairment <sup>3</sup> . . . . .	1.31	0.19	1.50	0.31	-1.19	2.22	0.24	2.46	2.10	-0.36	14.0	2.7
Average of 4 periods in 1932 after renal impairment . . . . .	0.27	0.79	1.06	0.30	-0.76	2.12	0.66	2.78	1.77	-1.01	14.4	4.2

\* Serum values for control group are merely approximate.

† Average values calculated from Farquharson, Salter, Tibbetts and Aub<sup>48</sup> of 14 3-day periods on 4 normal individuals on a neutral low-calcium diet.

VI. *Hartwich*.<sup>39</sup> Anatomical diagnosis "nephrocirrhosis arteriosclerotica."

VII. *Parreira and Castro-Freire*.<sup>7</sup> "Calcareous concretions in the kidneys, renal pelvis, and bladder."

VIII. *Wanke*.<sup>6</sup> "Granular contracted kidneys with marked calcium deposits in the calices."

IX. *Ask-Upmark*.<sup>40</sup> "There are considerable changes in the renal tissue with alteration of the smaller arteries as by arteriosclerosis, with a partly hyalin transformation of the glomeruli and with a noticeable atrophy of the convoluted tubules. There are, furthermore, numbers of calcium deposits situated in the distal parts of the tubular system (Scholtstucken and collecting tubules), in some places secondarily involving the interstitial tissue."

X. *Ask-Upmark*.<sup>41</sup> No history of chronic nephritis in this case. Kidneys were normal in size, but there were "in the cortex and especially in the pyramids several fine, yellowish, dry stripes of lime."



XI. *Bergstrand*.<sup>42</sup> A woman, aged 55, who had a high blood pressure on several occasions, although not consistently. The urine showed a trace of albumin and a specific gravity of 1.005 to 1.008. Autopsy: "The kidneys are somewhat diminished in size. The capsules are removed with difficulty. The surfaces are diffusely granular, reddish brown. The cortex is narrower than normal and of varying width." Microscopic examination: "In the kidneys the desquamated contents of the tubules as well as the hyalinized glomeruli show definite calcification of their media. Calcium deposits also occur interstitially. The calcification is most marked in the tips of the pyramids, where the deposits are macroscopically visible. Most of the glomeruli are completely or partly hyalinized. In others one sees capsular proliferation or increased number of cells in tubules. In a few places calcification in the outer leaf of Bowman's capsule was seen. The glomerular changes are consistent in every respect with those which one finds in nephrosclerosis."

XII. *Noble*.<sup>15</sup> Autopsy: Chinaman, aged 40. "The right kidney weighed 105 gm.; the cortex had an irregular gray area of scar tissue to which the capsule was adherent. The medulla and pelvis contained a few small calcified masses. Left kidney weighed 100 gm. and showed similar changes."

XIII. There can now be included in this series the patient with chronic nephritis and parathyroid tumor reported by *MacCallum*<sup>43</sup> in 1905, because a reexamination of the bones of that patient showed increase in size of Haversian canals and fibrosis of the bone marrow with many osteoclasts.\* The patient was a male, aged 26, who died in uremia after having suffered for several years with chronic nephritis and who showed at autopsy "chronic diffuse nephritis." It is of interest that this author wondered at the time if there was any relationship between the tumor and the nephritis, and even reported negative findings in the parathyroid glands in two other cases of chronic nephritis. This, we believe, was the first attempt to correlate chronic nephritis with parathyroid pathology.

We include in Type II, as a subgroup, 4 cases who died of chronic renal insufficiency and which showed at autopsy in addition to the chronic kidney lesions also calcium deposits in other soft tissues. We first included those cases under Type III, but it seemed more likely that the sequence was as follows: development of hyperparathyroidism, deposition of calcium in kidneys, development of renal insufficiency (Type II variety), retention of phosphates, and finally precipitation of calcium phosphate in other soft tissues as a terminal manifestation of chronic renal insufficiency—just as is sometimes seen in chronic nephritis without parathyroid disease (Schmidt<sup>49</sup>).

XIV. *Hoffheinz*, 1925.<sup>5</sup> Clinical diagnoses included that of "contracted kidneys." Non-protein nitrogen of blood was raised to 221 mg. with a blood pressure of only 85/55. The patient died in uremic coma. Autopsy: "Calcium metastases in the lungs; many calcium bodies and calcium infarcts in the kidneys. Besides a large coral-like stone filling the upper part of the right kidney pelvis, there were many small stones on both sides, the size of a pinhead to that of a lentil seed. Marked hydronephrotic dilatation of the right kidney pelvis with severe atrophy of the kidney tissue. Severe chronic hemopurulent pyelonephritis and cystitis with very marked areas of contraction in both kidneys (right kidney, 8.5 by 4 by 2.5 cm. in size, 85 gm. in weight; left kidney, 11 by 5.5 by 3 cm. in size, 120 gm. in weight)."

\* Personal communication from Dr. W. G. MacCallum.

This case was, furthermore, remarkable in that all the parathyroids showed tumor formation (see also Cases 11, 16 and 17).

XV. *Peneche*, 1926.<sup>44</sup> Clin. diag.: Chronic nephritis. Autopsy: "Contracted kidneys with calcium retention therein and extensive calcium metastases in the body. These were found especially in the muscle of the left heart, in the neighborhood of the orifice, in the auricle and apex of the heart, in the arteries of the thyroid, kidneys and spleen. The large vessels remained free. Furthermore, there were calcium concretions in the point of the tongue, skin and in the wall of the parathyroid tumor. Microscopically there were calcium concretions demonstrable in the examined glands of internal secretion."

XVI. *MacCallum* (unreported case\*). Johns Hopkins Hosp., No. 34560. Autopsy 11797. Male, aged 23. Symptoms (started in August, 1930): Nausea, weakness and vomiting; cleared after 1 week, but the patient never felt strong again. Polyuria and nocturia were noted. Blood pressure was 140/100. Red count was 2,500,000. The blood urea nitrogen was 185 mg. per 100 cc. The urine showed albumin, a few red and white cells. The specific gravity of the urine varied between 1.007 and 1.009. The patient died on January 12, 1931. No bone changes were found clinically. At autopsy there was extensive calcification of alveolar walls, bronchioles, and venules of lungs; lobular pneumonia; extreme chronic nephritis with calcification of tubules; hemorrhagic spots in stomach. Both lower parathyroids were enlarged (2 by 1.5 cm.). The bone of the vertebra was much rarefied; trabeculae in many places were eroded and excavated by a fibrous marrow tissue with numerous large osteoclasts.

XVII. Finally, mention must be made of the case reported by *Hubbard* and *Wentworth*<sup>45</sup> which most nearly falls into Type II, but which has certain features which make it entirely unique.

Male, aged 20. Clin. diag.: Chronic nephritis. Roentgen rays showed extensive calcification of peripheral arteries and deposits of calcium about the joints. The blood calcium was elevated. Autopsy: "Severe interstitial nephritis with a right hydronephrosis, calcium deposits in the wall of the left auricle, extensive and marked calcification of the smaller peripheral arteries, the arteries of the gastro-epiploic omentum, and the jejunum, but sparing the liver, spleen, lungs, kidneys and stomach, and osteitis fibrosa particularly marked in the skull, ribs and vertebrae, and two large parathyroid bodies, 2 cm. in diameter. . . ." The location of the calcium deposits is unusual in this case, although very much the same as in the case reported by *Peneche* (*v. supra*).

**Discussion.** Most of the points which we wished to bring out have been discussed in the subject matter, but there are a few entirely unrelated aspects which require further discussion.

The diagnosis of hyperparathyroidism immediately suggests severe bone lesions. It is probable, however, that the degree of bone involvement is an index to the duration of the disease, not to its severity. Therefore, it is not surprising that our only case of parathyroid poisoning had only slight bone disease. A rapidly developing tumor could theoretically kill a person from parathyroid poisoning without there being any bone lesions. A case has recently been operated upon in this clinic, and a tumor removed, in whom

\* Dr. W. G. MacCallum called this case to the attention of one of us and the notes were made directly from the hospital record and the autopsy protocol furnished by him.

there were no bone lesions by Roentgen ray and no elevation of blood phosphatase.

In English, in contrast to German, the term "nephritis" has been used for many conditions where no inflammation is thought to exist, and the term is almost synonymous with "renal insufficiency." If the same inaccurate nomenclature is to continue, "chronic parathyroid nephritis" might be applied to the Type II kidney lesions. The initial disturbance, however, is not an inflammation, but presumably a deposition of calcium. Therefore, the term chronic nephro-calcinosis would seem preferable. The same kidney lesions are found in other conditions, but the mechanism of their production is probably the same. (Thus patients with multiple myeloma often develop similar lesions [Perla and Hytner<sup>29</sup>].)

Under the general heading of prognosis and treatment, these are a few points which seem important. Obviously, one does not expect the sclerosed kidney of Type II to recover completely. The question is whether, once the cause has been removed, the condition will remain stationary in contrast to chronic glomerular nephritis or even show slight improvement. Our patient should answer this question in time. But preventive treatment is a real problem for the patient like C. M., who first enters with normal kidneys; on whom the parathyroid tumor is not found; and who later enters with impaired kidneys. Fluids should, of course, be forced in such a patient to keep the urine as dilute as possible. One might suggest giving ammonium chlorid to keep the urine acid, thus preventing deposits, but this is certainly contraindicated in view of the observation of Albright, Bauer, Ropes, and Aub,<sup>30</sup> that this drug very much enhances the decalcifying power of the parathyroid hormone. Furthermore, warning must be made that the two best indirect methods of combating the demineralization both increase the danger of kidney damage. Thus a very high-calcium diet may overcome the negative calcium balance, but this would tend to increase urinary calcium excretion. This tendency in the absence of renal damage is very slight, as shown by Bauer, Albright and Aub,<sup>3</sup> the urinary calcium of their patient with hyperparathyroidism being about the same whether the patient was on a high- or a low-calcium diet. Another theoretical danger of high-calcium diet in such a patient, however, is the possibility of producing parathyroid poisoning, just as so nearly happened in the patient of Hunter and Aub's,<sup>31</sup> when a low-calcium diet was changed to a high one, the dose of parathormone remaining constant. But more danger of renal involvement probably lies in the high-phosphorus diets suggested by Albright, Bauer, Claffin and Cockrill.<sup>14</sup> Such therapy is attended with a tremendous increase in phosphate excretion in the urine, coupled, to be sure, with a decreased calcium excretion. These authors warned against the possibility of kidney damage and suggested using sodium acid phosphate, so as to insure an



FIG. 1.—Roentgen ray of kidneys of case not discussed in this series who had hyperparathyroidism complicated by Type II kidney pathology. Calcium deposits can be seen to occur in collecting tubules, each pyramid being represented by a clump of calcium dots. This case was diagnosed and referred to us by Drs. Magendantz and Eddinger at the Boston Dispensary and will be reported in detail by them.

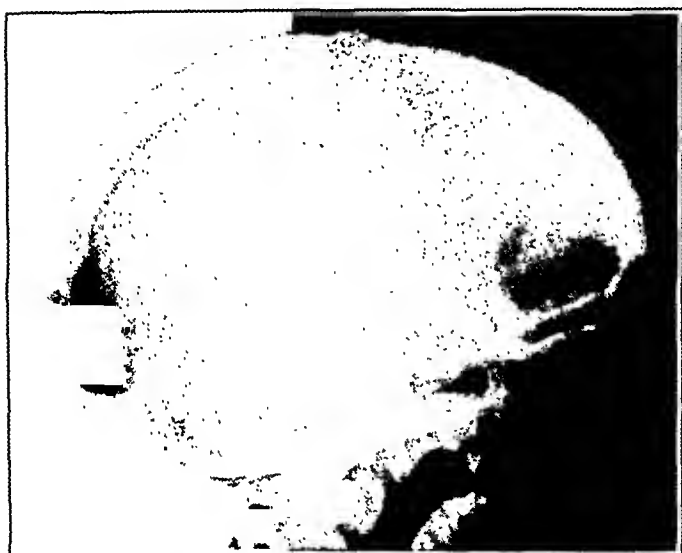


FIG. 3.—Roentgen ray of K. S. before operation, showing widening and irregularity of epiphyseal line.

*A*



*B*



*C*



FIG. 2.—Roentgen rays of skull of patient N. B., taken on July 28, 1930, October 4, 1930 and September 20, 1932, showing that decalcification responds to dietary treatment alone (see text).

acid urine. In the present state of our knowledge it would seem wise, given a patient with hyperparathyroidism in whom surgery has failed to remove the cause, to follow very carefully the serum calcium and phosphorus values during the instigation of either a high-calcium or a high-phosphorus diet, and to make sure that there is no tendency to the changes associated with parathyroid poisoning. The development of both a high serum-calcium and a high serum-phosphorus value should be regarded as a danger signal of parathyroid poisoning.

A good case to illustrate the possibilities and limitations of medical treatment is the patient N.B., previously reported<sup>14</sup> in connection with some phosphate ingestion experiments. She, in short, was a married woman, aged 41, who entered the hospital in 1930 with typical osteitis fibrosa cystica, bilateral renal stones, and the metabolic findings of hyperparathyroidism. Because no tumor was found at operation an effort was made to combat her disease with medical methods. Except for a short period of a high-phosphate diet, a high-calcium diet was used. This régime succeeded in recalcifying her skeleton, as is demonstrated in Fig. 2, which shows a series of Roentgen ray plates of her skull. But a check-up examination in 1932 revealed that she had developed definite kidney damage, with fixation of specific gravity and reduced phenol-sulphonaphthalein excretion. A parathyroid adenoma was removed at a second operation (Cope). Thus it would appear that the skeletal disease can be improved by medical means, but that kidney damage continues. The only satisfactory therapy, therefore, is surgery and, above all, surgery by a person who has made a special study of the problem. This aspect, however, is so important that it requires special consideration in a more appropriate place.

Patient K. S. showed a marked disturbance in the calcification of the subepiphyseal region by Roentgen ray (Fig. 3), suggesting that the zone of provisional calcification in the growing cartilage was being inadequately calcified. This has not been a feature of experimental hyperparathyroidism in animals, and the epiphyseal lines in the girl aged 14, reported by Amberg<sup>32</sup> and later by Pemberton and Geddie,<sup>21</sup> were normal. However, the published Roentgen rays on the boy aged 14 reported by Cosin<sup>19</sup> show somewhat similar changes. No mention of the epiphyseal lines in the girl aged 14, reported by Cooley,<sup>20</sup> was made. But before acalcification is added to decalcification as a feature of hyperparathyroidism because of this finding in K. S., it must be realized that some complicating factor may be entering into this case. Thus the possibility exists that the hyperparathyroidism caused the kidney damage, but that this in turn caused the acalcification of the growing epiphyses.

The association of such lesions in the epiphyses, together with renal changes naturally brought up the question of the as yet inadequately explained condition, renal rickets. Such a diagnosis

certainly seemed to fit K. S. When the true nature of her condition was revealed by operation, the question arose whether all so-called cases of renal rickets are not hyperparathyroidism with Type II renal lesions. However, from Mitchell's<sup>33</sup> excellent review of the subject of renal rickets, it seems almost certain that chronic renal insufficiency will in itself lead to rachitic-like changes in the skeleton. It appears equally certain, however, that, in several instances in the past where renal rickets has been diagnosed, an underlying hyperparathyroidism almost surely was present. The evolution of symptoms, for instance, in many of the quoted cases suggested that the skeletal symptoms antedated the renal. Furthermore, the Roentgen ray changes in the skeleton, the pathologic changes in the bones, the refractiveness to vitamin D, and the frequency of urinary calculi in cases of renal rickets all suggest the possibility of hyperparathyroidism. The fragmentary reports which are available concerning the blood calcium level in so-called renal rickets are rather against the suggestion that it is frequently due to hyperparathyroidism. The blood calcium levels tend to be depressed rather than elevated. There are a few cases of hypercalcemia, as the case with a level of 14.6 mg. reported by Parsons.<sup>34</sup> There is this to be said, however: We do not know whether an excessive amount of parathyroid hormone will maintain a high blood calcium in the presence of as severe phosphate retention as was present in most of the cases of renal rickets. It may be that just as hypophosphatemia is no longer a criterion of hyperparathyroidism in the presence of renal damage, so hypercalcemia may likewise cease to exist under such conditions. Preliminary observations on patients with chronic nephritis suggest that parathormone will not elevate their blood calcium levels.\* With this short survey, the subject must be left for further data. Certainly hyperparathyroidism with renal damage has masked under the name of renal rickets in some cases, but that all cases of renal rickets are so to be construed is highly improbable (see case with congenital cystic kidneys, etc.). Examination of the parathyroid glands at autopsy should settle the question in any one case. Mitchell's monograph gives no reference to such examination. Lathrope's case<sup>35</sup> showed normal parathyroid glands at autopsy.

One further possibility must be discussed. Could the changes in the parathyroid glands by any chance be secondary to the renal disease? This would only have to be considered in the few cases where multiple parathyroid glands were involved (*v. supra*—Cases XI, XIV, XVI, XVII). Since the parathyroid hormone raises blood calcium and lowers blood phosphorus, any influence opposing these actions might be attended by hyperplasia of the glands. A low-calcium intake, for example, causes hyperplasia.<sup>46,47</sup> It seems conceivable, therefore, that a chronic renal insufficiency with phosphate

\* Unreported data (Albright and Ellsworth).

retention and a high inorganic phosphorus level might likewise cause hyperplasia of all parathyroid tissue which might go on to multiple tumor formation. As far as the writer is aware, of all the cases with hyperparathyroidism, only those with kidney damage have shown multiple tumors. In these cases the kidney damage may be the cause and not the result of the parathyroid tumors.

**Summary and Conclusions.** 1. In hyperparathyroidism, calcium phosphate precipitates may cause three types of renal impairment depending on the locus of precipitation, *viz.*: Type I, precipitation in renal pelvis with resulting pyelonephritis; Type II, precipitation in renal tubules with resulting renal sclerosis, contraction and insufficiency; Type III, precipitation in kidney as one of several organs with acute renal failure, and death of undetermined cause in a few hours or days.

2. A review of 83 cases of hyperparathyroidism revealed 23 patients (27 per cent) with Type I lesions, 19 patients (23 per cent) with Type II, and 1 with Type III.

3. It is pointed out that the presence of a renal stone should suggest the possibility of hyperparathyroidism, and 2 cases are cited where this one finding led to such a diagnosis and the removal of a parathyroid adenoma in each instance.

4. The renal lesions of hyperparathyroidism can occur without bone lesions, the former being an index to the severity of the disease, the latter an index to its duration.

5. Metabolic studies were done on 2 patients with Type II lesions and revealed certain differences from the findings in similar studies on patients with hyperparathyroidism but without renal involvement, *viz.*: (a) Hypophosphatemia was not present; (b) the degree of hypercalcinuria was decreased; (c) the fecal calcium excretion was increased rather than decreased; (d) the partition of phosphorus in the urine as compared with the feces was less elevated.

6. Patients with Type II lesions often present a clinical picture very similar to that of chronic glomerular nephritis, but the scarcity of casts in their urinary sediment is a helpful differential point. The term nephro-calcinosis is suggested for this type of kidney lesion.

7. Following parathyroidectomy, the blood phosphatase level only gradually returns to normal, suggesting that the parathyroid hormone is not directly responsible for the production of the enzyme. Patients with hyperparathyroidism and no bone changes may have normal plasma phosphatase levels. The plasma phosphatase level is probably an index to the amount of bone disease and is independent of the degree of hyperparathyroidism.

8. Lesions in the growing epiphyses as shown by Roentgen ray suggestive of rickets were present in the patient here reported, and the question is raised whether so-called renal rickets may not often be hyperparathyroidism before closure of epiphyses complicated by



the Type II renal lesions. The evidence is almost conclusive that such is not always the case.

9. Whereas hyperparathyroidism can cause parenchymatous kidney damage, 3 cases are cited from the literature in which parenchymatous kidney disease was associated with multiple parathyroid tumors, and the question is raised whether in these instances the parathyroid hyperplasia was not secondary to phosphate retention dependent on the renal insufficiency.

10. As regards prophylactic therapy for the prevention of renal damage in hyperparathyroidism, it is pointed out that fluids should be forced; that an alkaline urine should be avoided; that ammonium chlorid and presumably other acidosis producing salts are contra-indicated; that a high-phosphorus diet, while indicated for the demineralization, imperils the kidneys and should be used only when the blood values can be carefully followed; and that the same applies to a high-calcium diet, although to a less extent.

11. A case of hyperparathyroidism is cited where medical treatment was followed by marked improvement of the bone condition, but where kidney damage eventually occurred; and the point of view is expressed that almost all patients with this disease will eventually develop kidney damage unless the condition is corrected by successful surgery.

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## A PHOTOGRAPHIC SUSPENSION STABILITY (SEDIMENTATION RATE) APPARATUS.

### (PRELIMINARY REPORT.)

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THE purpose of this paper is to describe a photographic recording instrument which it is felt will simplify and improve the sedimentation test, now so widely used.

The three principal methods for the determination of the sedimentation rate or suspension stability of blood are: I, *the time method*<sup>1</sup> in which the time required for the blood corpuscles to fall a certain distance is measured (*i. e.*, number of minutes required to fall 18 mm. in the Linzenmeier method); II, *the distance method* (2*a*, *b*, and *c*) in which the distance the blood corpuscles fall in a certain length of time is measured (*i. e.*, number of mm. at the end of 1 hour, 2 hours, or longer); III, *the graphic method* (2*c*) in which the distance of sedimentation of blood corpuscles is observed

continuously or at definite intervals for a given period of time (usually 1 hour).

Fåhræus,<sup>2</sup> Cutler,<sup>3</sup> Rourke and Ernstene<sup>4</sup> and others have investigated the graphic method. The following are the advantages of this method as summarized from the above work: (1) A characteristic line or curve is obtained, *i. e.*, horizontal, diagonal, and vertical lines and curves. (2) the steepness of the curves may be interpreted in terms of the severity of the disease. A diagonal curve is of much more serious import than a horizontal curve. The vertical curve usually indicates very marked disturbance; (3) changes in the curves during the course of an illness seem to have some prognostic significance and serve as an index of the patient's progress; (4) the straight line period of constant sedimentation may be observed and the period of most rapid fall of blood corpuscles may be evaluated therefrom (Rourke and Ernstene); (5) the periods of "aggregation" and "packing" may be observed.

The graphic method is not commonly used because it is troublesome and time consuming. By the photographic technique, the advantages of the graphic method are retained and the following disadvantages are eliminated: (1) The observer is not required to make constant or frequently repeated observations for the period of 1 or more hours; (2) the maximum number of determinations an experienced observer can do at the same time by the graphic method is three. By the photographic method the number of determinations is only limited by the size of the apparatus used; (3) the personal equation of the observer which may introduce an error is eliminated.

The present status of the numerous methods for the determination of the sedimentation rate and the use of the hematocrit have been briefly summarized by Wintrobe<sup>9</sup> who states "A variety of instruments have been employed for the determination of sedimentation rate." The presentation of another instrument therefore requires some justification because the multiplicity of techniques has already led to confusion. A disadvantage of the instruments commonly employed is that they can be used only for the determination of sedimentation rate. The employment of the hematocrit for this purpose is of special value because it has been demonstrated by several observers<sup>4,5</sup> that anemia magnifies and polycythemia minimizes the actual rate of sedimentation of the blood. If sedimentation is measured in a hematocrit, the volume of the packed red cells may subsequently be determined without further trouble. In this way an accurate measure of the degree of anemia or polycythemia is obtained and an appropriate correction can be made. A correction chart which is applicable to the instrument here described (Wintrobe hematocrit) is supplied by Rourke and Ernstene.<sup>4</sup>

"The hematocrit is filled to the '10' or '0' mark. For the determination of sedimentation rate the fall in the upper level of red cells is measured in millimeters by the calibrations and numbers at the left of the scale. . . . There is considerable debate

whether the single observation of the distance which the red cells have fallen at the end of 1 hour is an adequate test of the suspension stability of the red corpuscles. The instrument described is, however, suitable for the 'time,' 'distance,' or 'graphic' procedures. . . ."

The Photographic Suspension Stability Apparatus here described employs the Wintrobe hematocrit. The above statements are, therefore, equally applicable to the photographic method.

The sedimentation procedure causes no loss of time in hematocrit determinations, since it is an advantage to allow the hematocrit to remain standing for 1 hour before centrifugation in order to permit settling of the colorless corpuscles and platelets in the uppermost layer of the hematocrit as pointed out by Wintrobe.<sup>9</sup>

**General Principle and Description of Apparatus.** The principle of the photographic suspension stability apparatus is based on the difference in density to light between plasma and plasma plus blood corpuscles in a glass vessel. The intensity of the light is adjusted so that plasma will transmit, while plasma plus blood corpuscles will not transmit light. When a tube containing blood to which an anticoagulant\* has been added is allowed to stand, the height of the column of plasma will increase with time, while that of the blood corpuscles will decrease. When light, as above described, is projected upon such a tube, the plasma will transmit the light, while the portion of the column containing plasma plus blood corpuscles will not transmit light.

The blood-filled glass tubes are inserted in the walls of an octagon or square housing (serving as a camera). Within the housing is a kymograph drum propelled by a low speed clock mechanism. Light sensitive photographic paper is fastened to the drum. The paper is thus in constant motion and the light transmitted by the plasma makes a continuous record on the photographic paper. Upon completion of the determination, the photographic paper is removed, developed and fixed, thus presenting a permanent, accurate and continuous record of the suspension stability or "sedimentation" of the specimen of blood (Plates I and II).

Figures 1 and 2 are vertical and plan views of the apparatus. Figure 3 is a vertical view of one side of the housing. Figures 4 and 5 are vertical and plan views of the receptacles with the hematocrits in place.

**Detailed Description of Apparatus.** The housing consists of a "light-tight" wooden box surrounding the kymograph drum. This serves as a camera obscura. The inner surface of the center of each face (side) of the housing is at a distance of 2 mm. from the surface of the drum (Fig. 2). There are three receptacles (*R*) in each face of the housing and they are located in the approximate vertical centers of the faces (Fig. 3). These receptacles (*R*) are rectangular wooden blocks capable of receiving hematocrits filled with blood. They can be inserted in slots in the housing and may also be easily removed.

\* For effect of different anticoagulants and quantity of anticoagulant on suspension stability, see Rourke and Plass.<sup>6</sup>

Figure 4 is a vertical view and Fig. 5 a horizontal section of the receptacle, 150 by 35 by 25 mm., with the hematocrit *in situ*. In the receptacle there is a bore 6.5 mm. in diameter and 123 mm. in height for the hematocrit. In the top of the receptacle and centered in same is a bore 28 mm. in diameter and 15 mm. deep. The latter bore accommodates the thumb, index finger, and hematocrit, enabling one to place the latter in the receptacle.

*SI* is a slit 1 mm. wide extending for a distance of 70 mm. below the level

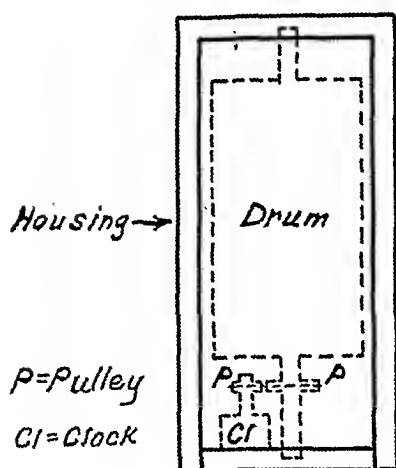


FIG. 1.

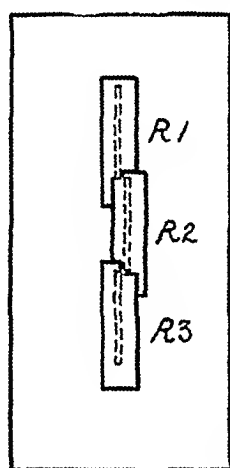


FIG. 2.

FIGS. 1 and 2.—Vertical and plan views of the photographic suspension stability (sedimentation rate) apparatus.

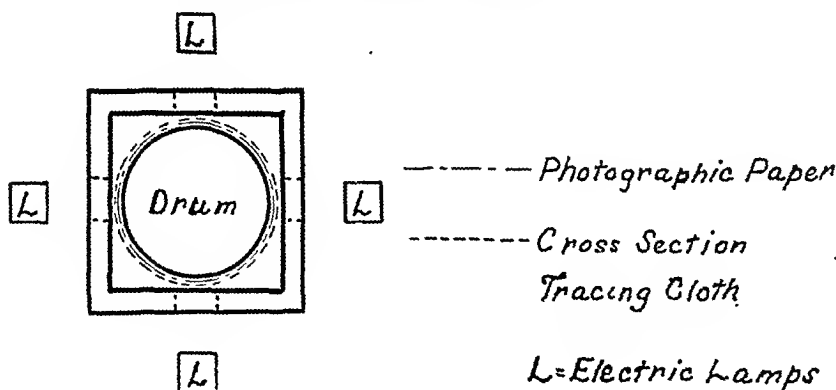


FIG. 3.

FIG. 3.—Vertical view of one side of the housing.

of the blood in the hematocrit (*i. e.*, the 100-mm. mark). The light from source (*L*) is projected upon the slit and thereby upon a narrow column of blood in the hematocrit. With the sedimentation of the blood corpuscles, the light transmitted affects the photographic paper. It is shown as the large black area in Plates I and II.

*SII* is a slit 1 mm. wide and 3 mm. long extending from 2 to 5 mm. above the level of the blood in the hematocrit. This slit constantly transmits a narrow beam of light and thereby indicates the start, duration and end of the experiment. The 3 mm. heavy upper line in Plates I and II is the result

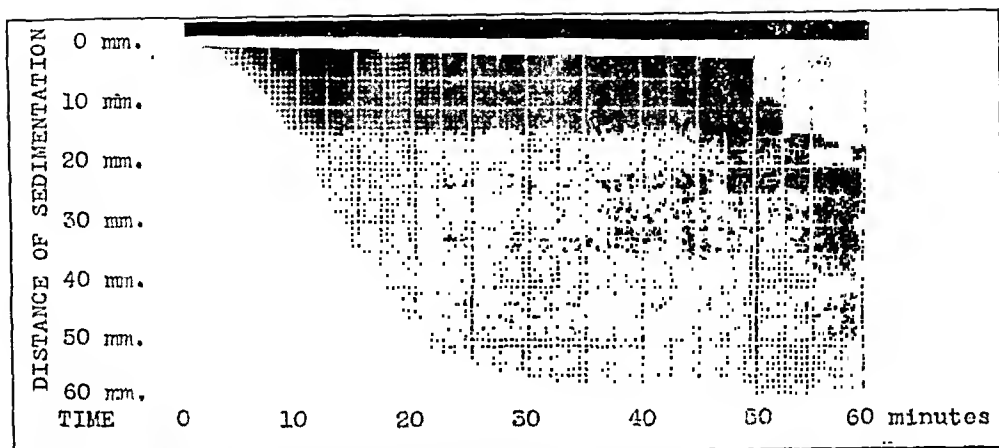


PLATE I.

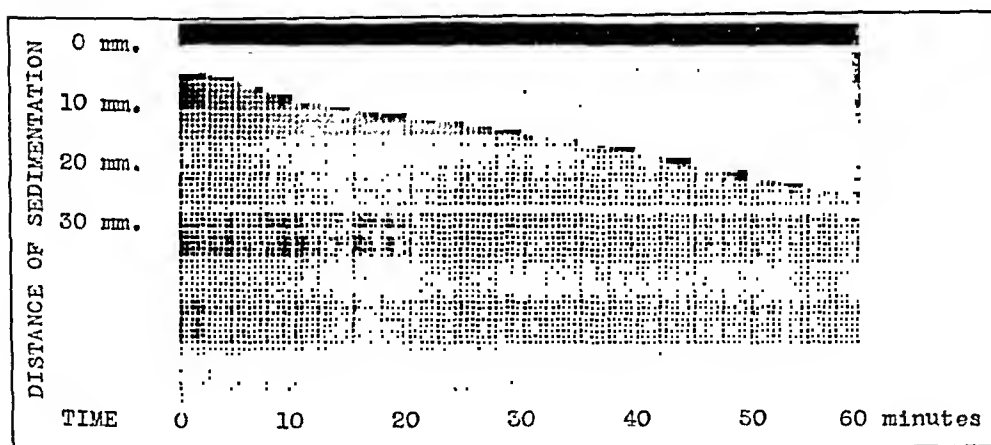


PLATE II.

PLATES I AND II.—Photographic records of the suspension stability or sedimentation rate of two specimens of blood.



of this exposure. This is important, since during the period of aggregation which occurs in the first phase of the sedimentation, there is little or no fall of the blood corpuscles.

A number is cut through the outer portion of the receptacle, just to the left of the receptacle in the manner of a window. This number is covered by a small elliptical aluminum disk. The disk is fastened to the receptacle by means of a pin eccentrically placed and may be turned about this pin. The disk is rotated to one side and the electric lights are turned on for a period of 30 seconds before the hematocrit is inserted in the receptacle. This procedure exposes the photographic paper to the number by which it may be identified.

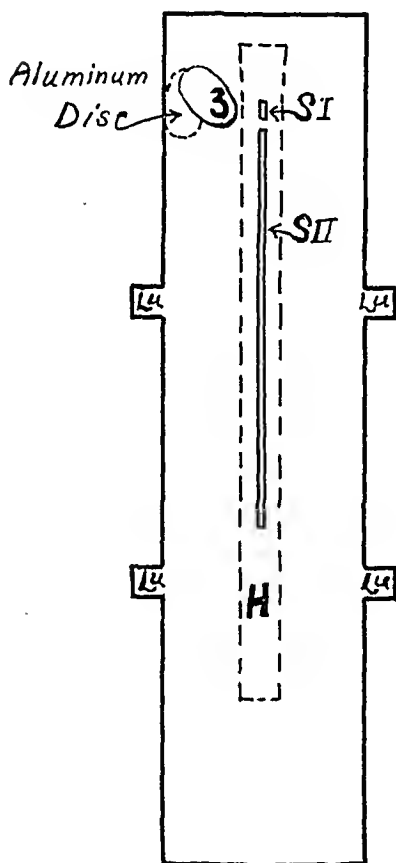


FIG. 4.

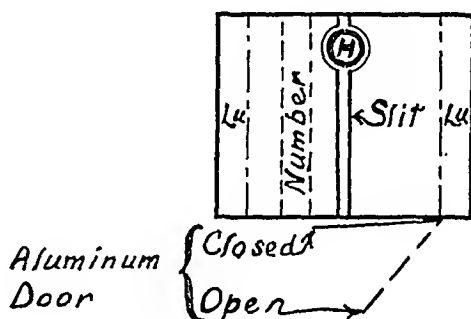


FIG. 5.

Figs. 4 and 5.—Vertical and plan views of the receptacle with the hematocrits in place.

A rectangular aluminum door 150 by 22 mm. covers the slits when the instrument or any receptacle is not in use. While the instrument is in operation, the aluminum door covers the slits of the receptacle not in use, and they may be swung aside at any time that one desires to set up a sedimentation test in these receptacles.

The kymograph drum is similar to those used in physiologic work. The preferable diameter is from 18 to 25 cm. The height of the drum will depend on the number of determinations one desires to carry out at the same time. For the Wintrobe hematocrit filled to the 100-mm. mark, one



should allow 70 mm. height of the drum for each row of receptacles. This height seems adequate for in our work, using oxalate as an anticoagulant, the maximum fall of blood corpuscles which was observed in 1 hour was 60 mm.

The drum is driven by motion transmitted from a clock.\* Ordinary alarm clocks\* are very satisfactory for this purpose. The crystal, dial, and hands are removed from the clock. A small hole is made in the center of a No. 2 gum rubber stopper and the hour-hand pinion of the clock is forced into this hole. A piece of copper wire is placed around the stopper and tightened in the manner of a twisted ligature. A pulley is attached to the pinion of the kymograph drum and contact is made between this and the rubber stopper attached to the clock by means of a soft rubber or leather belt. The motion from the clock is thus transmitted to the drum. The pulleys are adjusted in ratio to permit a point on the surface of the drum to travel at the rate of 120 mm. per hour. Gears are preferable in place of the belt and pulley arrangement, but this increases the cost of the instrument.

A high-contrast, light-sensitive photographic printing paper† such as is used in commercial photography is fastened to the drum. Cross-section tracing cloth is fastened over the photograph paper and in close contact with and surrounding same. In our work a mesh of one square millimeter was used, since it is a standard ware. If the use of such a fine mesh is confusing, linen tracing cloth may be ruled with India ink in any desired ruling. The tracing cloth may be used over again and if care is taken may be used for several hundred determinations.

An interval-timer electric switch‡ makes contact with the light circuit and is also connected with a pulley in contact with the belt of the clock mechanism. The lever of the timer must be pushed to start the instrument and it is set to stop the clock mechanism and break the circuit of the electric lamps, 1 hour after the last sedimentation is set up.

**Directions for Operation of Apparatus.** Photographic paper surmounted by cross-section tracing cloth is fastened to the kymograph drum. The aluminum disks covering the numbers are rotated to one side and the electric lights are turned on for a period of 30 seconds; the Wintrobe<sup>7</sup> hematocrit is filled to the 100-mm. mark with blood to which an anticoagulant has been added; the hematocrit is inserted at once in the receptacle (*R*) in the housing; the battery of electric lights (*L*) is turned on; the aluminum cover (*Al*) is turned aside; and the clock mechanism is started. The lever of the interval-timer electric switch is set to stop the instrument at 1 hour (or other desirable time) after the last hematocrit is inserted.

The photographic paper is removed and developed any time after the last determination is completed. The hematocrits are removed, centrifuged, total volume of packed red cells determined and correction in sedimentation rate is made for the degree of anemia or polythemia.

\* Slow speed kymograph drums may be used but they are quite expensive.

† A simpler method may be employed when fewer determinations are made at the same time. Electrocardiographic paper is exposed in the cross-section mechanism of the electrocardiograph. The paper is then loaded on the kymograph drum and the paper is exposed to the beam transmitted by the plasma as described above. This will give a suitable cross hatching upon development. However, due to the narrowness of the paper, a separate strip (of paper) is required for each row of four hematocrits. This plan may be carried out more extensively by first exposing large sheets of photographic paper, eliminating the use of tracing cloth.

‡ The interval-timer electric switch may be purchased from the Arthur H. Thomas Company, Philadelphia.

Since devising this apparatus, I have discovered a paper by Litten<sup>8</sup> whose apparatus is similar to the one here described. However, his apparatus is relatively more expensive, less automatic in operation, and only one sedimentation determination may be carried out at a time.

**Summary.** A photographic suspension stability apparatus based on the difference in density to light between plasma and plasma plus blood corpuscles has been described. Light is projected through the plasma in blood-filled hematocrits upon light sensitive photographic paper which is in constant motion. The photographic paper is later developed and fixed, thus presenting a permanent, accurate and continuous record of the suspension stability of the blood. The apparatus has the advantages that it is self-recording; it requires no attention after it has been started; the number of determinations is only limited by the size of the instrument; and the records are free from the personal equation of an observer.

The author wishes to express his sincere appreciation for the kind assistance and coöperation of Dr. M. M. Wintrobe, who has assisted in the work with innumerable suggestions and supervised the preparation of the manuscript.

J. H. Emerson of Cambridge, Mass., is prepared to supply the instrument described in this paper.

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### THE HEMATOPOIETIC RESPONSE OF THE RAT TO INJECTIONS OF PENTNUCLEOTIDE, AND ITS RELATION TO THE TREATMENT OF AGRANULOCYTOSIS.

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FOLLOWING the work of Jackson,<sup>1</sup> who first demonstrated the existence of pentose nucleotides in normal blood, derivatives of nucleic acid in various forms have been used in the treatment of neutropenic states. The latest preparation, known commercially as pentnucleotide, is being employed widely in cases of agranulo-



Rat No.

Rat No.	Date.	Peripheral blood.						Bone marrow.											
		W.B.C.	Poly. neutrophils, per cent.		Lymphocytes, total per cent.	Lymphocytes, per cent.			Eosinophils, per cent.	Poly. neutrophils, per cent.	Eosinophils, per cent.	Lymphocytes, per cent.	Myeloblasts, per cent.	Myelocytes, per cent.	Erythroblasts, per cent.	Reticulocytes, per cent.			
			Mature.	Band forma.		Y	M	O											
1.	Before Dec. 19	2800	10	..	87	68	28	4	..	3	52.0	0.8	12.8	1.4	18.8	14.2	14.2		
2.	After Jan. 10	7200	16	..	84	14	61	25	..	..	32.4	..	19.8	3.6	22.0	22.2	5.4		
3.	Before Dec. 19	6600	25	..	84	35	52	13	1	..	32.4	..	19.8	3.6	22.0	22.2	7.3		
4.	After Jan. 10	6600	14	..	82	27	59	14	4	4	19.8	0.6	21.8	4.6	28.0	25.2	6.2		
5.	Before Jan. 11	7800	20	..	74	35	43	22	4	2	19.8	0.6	21.8	4.6	28.0	25.2	5.0		
6.	After Jan. 11	5400	2	..	98	51	39	10	..	..	39.6	..	18.6	2.4	21.6	18.2	5.4		
7.	Before Jan. 19	7000	12	..	86	25	69	6	2	..	39.6	..	18.6	2.4	21.6	18.2	2.0		
8.	After Jan. 11	6200	10	..	90	47	42	11	..	..	24.8	0.8	14.4	3.6	20.8	35.6	5.0		
9.	Before Jan. 19	6000	2	..	96	22	56	22	..	2	24.8	0.8	14.4	3.6	20.8	35.6	5.4		
10.	After Jan. 11	8200	12	..	84	30	57	13	2	..	21.0	0.8	23.6	3.6	30.0	21.0	4.4		
11.	Before Jan. 19	6800	12	..	84	0	60	40	6	..	21.0	0.8	23.6	3.6	30.0	21.0	4.2		
12.	After Jan. 12	4800	26	..	68	38	50	12	..	2	42.6	0.8	18.2	1.8	16.4	20.2	3.4		
13.	Before Jan. 19	5000	28	..	70	37	47	16	..	..	42.6	0.8	18.2	1.8	16.4	20.2	3.6		
14.	After Jan. 11	7000	6	..	94	27	57	16	..	..	20.0	0.4	19.6	6.8	28.2	25.0	3.9		
15.	Before Jan. 6	4000	30	..	88	45	45	10	..	..	20.0	0.4	19.6	6.8	28.2	25.0	7.6		
16.	After Jan. 15	4300	26	..	70	62	34	4	2	..	25.8	..	36.8	2.8	17.0	17.6	8.0		
17.	Before Jan. 11	6200	10	..	90	43	51	6	..	..	25.8	..	36.8	2.8	17.0	17.6	8.2		
18.	After Jan. 19	5000	14	..	86	25	59	16	..	..	17.6	..	29.4	4.6	20.4	28.0	5.0		
19.	Before Feb. 1	4800	9	..	87	22	64	14	3	1	28.4	0.8	16.8	3.0	18.2	32.8	5.5		
20.	After Feb. 10	4600	18	..	78	16	68	16	2	2	28.4	0.8	16.8	3.0	18.2	32.8	5.6		
21.	Before Feb. 1	4800	5	..	95	18	61	21	..	..	32.4	0.4	12.8	4.0	19.8	30.6	6.2		
22.	After Feb. 10	5600	16	..	84	14	62	24	1	1	32.4	0.4	12.8	4.0	19.8	30.6	5.8		
23.	Before Feb. 1	7400	16	..	82	29	51	20	..	..	32.4	0.4	12.8	4.0	19.8	30.6	6.4		
24.	After Feb. 10	5400	14	..	85	26	42	32	..	1	32.4	0.8	18.4	2.6	21.4	24.4	6.8		
25.	Before Feb. 1	4800	14	..	82	30	62	8	4	..	32.4	0.8	18.4	2.6	21.4	24.4	6.8		
26.	After Feb. 10	6600	22	..	78	20	65	15	9	..	36.4	0.4	18.2	2.2	14.8	28.0	4.8		
27.	Before Feb. 1	5200	22	..	68	27	48	25	..	1	36.4	0.4	18.2	2.2	14.8	28.0	5.2		
28.	After Feb. 10	6600	16	..	79	30	52	18	4	1	27.2	0.3	20.0	4.5	15.3	32.7	5.6		
29.	Before Feb. 1	3400	26	..	72	25	58	17	2	..	41.3	..	11.9	3.8	17.0	26.0	4.3		
30.	After Feb. 10	5100	15	..	82	40	47	13	3	..	41.3	..	11.9	3.8	17.0	26.0	7.1		
31.	Before Feb. 1	4800	32	..	56	17	53	30	12	..	18.0	0.6	29.2	4.0	20.0	28.2	8.0		
32.	After Feb. 10	4800	25	..	71	32	43	25	1	3	18.0	0.6	29.2	4.0	20.0	28.2	8.7		
		Average "Before" 5300 14.6.																Average "After" 6000 17.1.	

cytosis. Jackson<sup>2</sup> and his coworkers have reported very good results from this method of therapy, while Rosenthal,<sup>3</sup> Fitzhugh and Comroe<sup>4</sup> consider these preparations to be of doubtful value.

A study of the bone marrow in cases of agranulocytosis has revealed that it can be either aplastic or hyperplastic. Fitzhugh and Krumbhaar<sup>5</sup> suggest a maturation arrest as the fundamental pathologic basis in those cases which show a hyperplastic marrow. The pentose nucleotides are supposed to have a positive chemotactic and maturative effect on myeloid foci and should therefore improve the delivery of granular leukocytes to the peripheral circulation.

Our own clinical experience with pentnucleotide has not been very conclusive, and it seems to us that those cases of agranulocytosis which improved after injections of this substance might have recovered as well without its use.

With these facts in mind, we decided to try the effects of pentnucleotide on the blood and bone marrow of an animal whose peripheral circulation is normally in a neutropenic state. Young rats were found to answer this requirement, as their blood normally shows a leukopenia with a low relative percentage of polymorphonuclear leukocytes. On one group of animals the effects of repeated injections of large doses of pentnucleotide alone were studied, while in another group the bone marrow was first depressed with benzol before the nucleotide was injected. Control groups of rats in which saline was injected instead of nucleotide were run at the same time. The peripheral blood and bone marrow were examined in each case for evidence of stimulating or maturative effects of the injections on the blood cells.

In the blood the Schilling count, lymphocytic index<sup>6, 7</sup> and reticulocyte percentage were employed as criteria of these changes, while the bone-marrow cells were studied in smears.<sup>8, 9</sup>

**Technique.**—The rats used were about 4 to 6 weeks old. For the experiment with nucleotide alone, single counts were done on all the animals before the injections were begun. One-half was then given daily injections of 1 cc. of pentnucleotide for 7 days, while the controls were given 1 cc. saline daily for the same length of time. Counts (single) were then repeated on the entire group and they were killed and bone-marrow smears made from the femur. For the experiment with benzol and nucleotide, another group of rats was selected and all were given daily injections of  $\frac{1}{2}$  cc. of benzol in olive oil until the total leukocyte count in the blood was about 400. This required about 7 injections. Several of these rats were killed and the bone-marrow was found to be almost devoid of polymorphonuclear leukocytes. One-half of the remaining group was now given daily injections of 1 cc. of pentnucleotide for 7 days and the other half was given 1 cc. of saline for the same length of time. Counts were then done and bone-marrow smears made as above. In doing the differential count, Wiseman's<sup>6</sup> Wright-Giemsa stain was employed and the polymorphonuclear leukocytes were classified according to the Schilling index, while the lymphocytes were divided into Y, M, and O forms to determine their state of maturity. The reticulocytes were studied on fixed preparations vitally stained with cresyl blue and counterstained with Wright's stain, 1000 red cells being

examined in making the counts. The bone-marrow smears were made on slides and stained with Jenner-Giemsa stain, the Giemsa stain being left on the slide for  $\frac{1}{2}$  hour. A differential count of 1000 cells was done using a square diaphragm in the ocular, such as is used in enumerating reticulocytes.

TABLE 3.—RATS INJECTED WITH BENZOL FOLLOWED BY NUCLEOTIDE.

Rat No.	W.B.C.	Peripheral blood (final count).							Bone marrow.						
		Poly. neutrophils, mature per cent.	Lymphocytes, total per cent.	Lymph., per cent.			Monocytes, per cent.	Eosinophils, per cent.	Reticulocytes, per cent.	Poly. neutrophils, per cent.	Eosinophils, per cent.	Lymphocytes, per cent.	Myeloblasts, per cent.	Myelocytes, per cent.	Erythroblasts, per cent.
				Y	M	O									
1	2400	42	48	51	39	10	10	..	4.6	12.2	1.4	27.6	10.0	22.8	26.0
2	1700	28	66	25	49	26	6	..	6.8	24.0	1.0	31.8	9.2	23.8	10.2
3	1100	34	58	20	60	20	8	..	1.4	28.4	0.6	31.2	7.2	12.0	20.6
4	3200	60	32	54	44	2	8	..	6.2	32.2	0.2	21.0	3.8	12.4	29.4
5	3400	26	62	26	48	26	12	..	5.8	32.2	0.4	18.8	4.8	16.2	27.6
6	2800	44	40	55	39	6	14	2	7.4	26.0	0.8	24.8	4.8	14.2	29.4
7	1900	22	67	40	36	24	11	..	2.2	14.0	0.8	24.4	9.8	23.2	27.8
8	2000	31	63	32	49	19	6	..	4.6	34.6	0.8	19.4	6.2	18.0	21.0
9	1400	42	56	53	45	2	2	..	2.4	19.2	0.8	24.8	9.2	21.0	25.0
10	1600	46	44	12	50	38	8	2	8.2	36.2	0.2	14.0	4.8	16.2	38.6
11	5400	19	76	27	54	19	4	1	5.6	32.4	0.4	18.8	6.2	19.0	23.2
12	6700	32	66	19	63	18	2	..	7.2	26.8	0.2	21.4	3.2	19.8	28.6
Av.	2800	35.5													

RATS INJECTED WITH BENZOL FOLLOWED BY SALINE.

1	800	22	68	40	35	25	10	..	1.8	0.8	0	55.4	10.2	3.2	30.4
2	3600	64	30	8	60	32	6	..	3.4	33.0	1.0	22.2	4.8	14.2	24.8
3	2600	60	36	24	52	24	4	..	4.2	34.2	0.4	24.2	4.2	18.8	18.2
4	2100	36	60	45	47	8	4	..	3.2	14.0	1.0	25.2	8.2	18.8	32.8
5	1800	28	64	32	52	16	8	..	3.4	28.2	0.4	21.4	5.2	19.8	25.0
6	4600	24	70	33	56	11	6	..	6.6	34.0	0.4	19.8	4.2	18.2	23.4
7	3000	46	36	42	48	10	8	..	6.4	26.8	0.6	22.4	8.2	16.8	25.2
8	2300	34	61	18	49	33	5	..	6.8	31.4	0.8	18.0	4.8	19.2	25.8
9	2900	31	59	21	52	27	8	..	6.2	25.2	0.2	20.0	5.8	15.1	33.7
10	1700	40	56	30	45	15	4	..	5.8	28.2	1.1	21.2	7.4	15.0	27.1
11	3100	35	55	27	40	13	10	..	7.1	32.7	0.7	15.8	9.4	19.0	22.4
12	1500	24	69	36	35	29	7	..	4.5	13.0	0.3	25.7	6.3	20.3	34.4
Av.	2500	37													

The experimental data follow:

A study of the experimental data is rather surprising, because it reveals that in the case of the rat, injections of pentnucleotide have very little effect in stimulating or improving the maturation of the blood cells. The total white count, Schilling and lymphocytic indices, reticulocyte percentage and bone marrow differential react about the same after saline injections as after nucleotide. Regeneration after benzol poisoning occurs just as quickly with saline injections as with nucleotide.

This experimental finding is somewhat of a disappointment, because the theory expressed by Doan,<sup>10</sup> attributing to nucleic acid and to the nucleotides chemotactic, maturative and initiatory stimuli for neutrophil myelocytes, seemed to explain the beneficial action of blood transfusions and irradiation on agranulocytosis as

well. Blood transfusions were supposed to be helpful in that they supplied additional nucleotides to a circulation deficient in this respect. Small doses of Roentgen ray might act in causing a primary destruction of some of the intact myeloid foci with a liberation of autogenous nucleotide, which then could initiate the maturation and delivery of leukocytes from the remaining myeloid foci. Isaacs<sup>11</sup> has shown that Roentgen rays have a maturing effect on all types of blood cells, the myeloid, lymphoid and erythroid. If the Roentgen ray acts through the nucleotide mechanism, it seems logical that injections of nucleotide would improve the maturation of red cells as well as polymorphonuclear neutrophils. This has not been the case in our work. The doses of nucleotide were very large in proportion to the weight of the rats and should have been sufficient to cause the changes expected. It can be argued that the hematopoietic system of the rat is different from that of man, but if the rat's bone marrow was depressed by benzol just as in the case of man, it ought to be stimulated by the same agents which are supposed to stimulate the human bone marrow. It is further recognized that other possible variants prevent the deductions from the experiment from being applied unqualifiedly to the treatment of human agranulocytosis. It is conceivable that an agent might be potent for neutropenia produced in one way and not for that produced in another; it might restore a lowered count to normal but not raise a normal count above normal, and so on.

However, these findings emphasize the vital importance of adequate controls, may help to throw light on some of the disappointing results obtained in the treatment of agranulocytosis with nucleotide and may also lend support to those who believe that many cases of agranulocytosis recover by themselves, and that a large percentage of the beneficial results attributed to the various forms of therapy for this condition may just be coincidental.

**Conclusions.** 1. The stimulating and maturative effect of injections of pentnucleotide on the hematopoietic system of the rat was studied, both with and without preliminary benzol depression.

2. Control injections of normal saline produced results not significantly different from those of the nucleotide.

3. The practically negative experimental results cast some doubt on the value of pentnucleotide in the treatment of agranulocytosis.

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## AN ANALYSIS OF SO-CALLED APLASTIC ANEMIA.

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"APLASTIC" anemia is usually regarded as a well-defined, readily recognizable clinical entity. The more important clinical and hematologic features are thought of as being a direct result of progressive depression and final cessation of bone marrow activity, and aplasia of this tissue is the accepted pathologic finding.

Our experience leads us to believe that the classical criteria of aplastic anemia exclude from that category many cases of the same fundamental nature as those included therein. In a series of 13 cases, representing the total experience of this clinic during the last 15 years, evidence of blood regeneration was a common finding. Nevertheless, our study of these cases and review of the literature indicate that they are not essentially different from many cases ordinarily classed as "aplastic anemia." Of these cases 2 followed exposure to benzol, 1 was apparently associated with prolonged exposure to Roentgen rays, while in the remaining 10 no contact with any known marrow poison was found and the clinical diagnosis of idiopathic aplastic anemia was made.

The clinical features of all were similar, the outstanding feature being a progressive depletion in the number of circulating red cells, white cells and platelets. Evidence of regeneration appeared in all, with variation in size and shape of the red cells, increased reticulocyte counts, and occasional normoblasts as evidence of erythrocytic activity. In all a shift to the left of the white cells suggested leukocytic activity.

Study of the bone marrow revealed a wide variation in microscopic appearance. In 3 there was obvious hypoplasia of the bone marrow elements. In 2 the marrow appeared normal. In 2 moderate hyperplasia was seen and in the remaining 6 definite and marked hyperactivity was noted. The individual cases will be briefly presented, to be followed by an analysis and summary of the various findings.

**Case Abstracts.** CASE 1 (No. S0886). An Irish man, aged 53, admitted to the wards with a 3 months' history of progressive weakness and pallor. On admission there was moderate emaciation, extreme pallor, no purpura, and an enlarged spleen palpable just below the costal margin.



## THOMPSON, RICHTER, EDSALL: APLASTIC ANEMIA

R. B. C., 1,800,000; Hgb., 32 per cent; W. B. C., 1200; Pmn., 20 per cent; platelets, 77,000. There was marked variation in the size, shape and staining of the red cells and occasional normoblasts were seen. Notwithstanding the small number of neutrophils there was a definite shift to the left, with occasional myelocytes and rare myeloblasts. In spite of 8 transfusions and large amounts of liver extract and iron, the course was progressively downhill, and he died 6 months after the onset of symptoms, with a final clinical diagnosis of idiopathic aplastic anemia. At *autopsy* the femur marrow was found to be cellular with normal marrow elements appearing in normal numbers and in normal distribution. Examination of the other organs showed no anatomic basis for the hypocythemia.

CASE 2 (No. 233329).—A Jewess, aged 37, was admitted with 2 months' history of progressive weakness and pallor. There had been no contact with any known industrial or chemical poisoning. On admission the patient presented extreme pallor but no evidence of loss of weight. Menorrhagia appeared and persisted and occasional petechiæ were noticed. The spleen could not be felt. R. B. C., 750,000; Hgb., 20 per cent; W. B. C., 2000; Pmn., 47 per cent; platelets, 22,000. There was moderate variation in size, shape and staining of the red cells with occasional myelocytes were seen. In *autopsy* was very cellular, showing abundant blood formation, with many clusters of nucleated red cells in various stages of development, many "stem cells," a normal or slightly increased number of myelocytes of all types and a slight reduction in megakaryocytes. Examination of the other organs showed no anatomic basis for the hypocythemia.

CASE 3 (No. 276310).—An American physician, aged 70, who for any years had been engaged in experimental work with Roentgen rays and had had 1 finger removed following a carcinomatous change in a Roentgen ray burn, came into the hospital with a 5 months' history of increasing weakness, dyspnea, and pallor. There had been no loss of weight and no purpura. R. B. C., 2,000,000; Hgb., 50 per cent; W. B. C., 1400; Pmn., 32 per cent; platelets, 39,000. There was moderate variation in size and shape of the red cells and normoblasts were seen in all the smears. There was a distinct shift to the left in the white cells, with occasional myelocytes and rare myeloblasts. A reticulocyte count was not done. In spite of 4 transfusions and nucleic acid by mouth, the patient failed rapidly and died 6 months after the onset of symptoms. The final clinical diagnosis was aplastic anemia, secondary to Roentgen ray poisoning. At *autopsy*, marrow from the femur showed definite hyperplasia, with a moderate increase in the number of developing cells of the red and white cell series and marked increase in the number of megakaryocytes. There was, in addition, a muscular dystrophy of the Charcot-Marie-Hoffman-Tooth type. Examination of the other organs showed no anatomic basis for the hypocythemia.

CASE 4 (No. 326119).—A Polish Jew, aged 48, entered the hospital with a 3 weeks' history of rapidly progressive weakness and pallor. There had been no loss of weight. The spleen was not enlarged. There were many petechiæ, but no ecchymoses. R. B. C., 1,500,000; Hgb., 35 per cent; W. B. C., 2500; Pmn., 12 per cent; platelets, 69,000. There was moderate variation in size and shape of the red cells and nucleated red cells appeared in numbers varying between 1 and 5 per hundred W. B. C. Reticulocytes, 1 per cent. There was a marked shift in the white cells and shortly before death 30 per cent myeloblasts were found. In spite of 2 transfusions and

several intramuscular injections of nucleotide, the patient failed rapidly and died 1 month after the onset of symptoms. Although it was felt that the clinical diagnosis was probably aplastic anemia, the possibility of acute leukemia was seriously considered. At *autopsy*, marrow removed from a rib and femur showed moderate hypoplasia, all the elements being present, but in reduced numbers. There were many plasma cells in both femoral and rib marrows and an increased amount of fat. There were no changes suggesting acute leukemia. Examination of the other organs showed nothing of note.

CASE 5 (No. 298171).—A Greek stamp collector, aged 37, was admitted with a 4 months' history of progressive weakness and pallor. There had been no loss of weight and no bleeding. There was no enlargement of the spleen and lymph nodes. R. B. C., 1,200,000; Hgb., 20 per cent; W. B. C., 1400; Pmn., 49 per cent; platelets, 9000. There was moderate variation in size and shape of the red cells, the reticulocytes varied from 0.1 to 1.4 per cent and rare normoblasts were seen throughout the course. There was a persistent, though variable, increase in the number of young granulocytes. A terminal increase in myeloblasts up to 28 per cent of the white cells strongly suggested acute leukemia in the aleukemic phase. In spite of repeated transfusions, large amounts of liver and liver extract, nucleic acid and iron, there was a progressive, slow decrease in the number of cellular elements in the blood, and the patient died 13 months after the onset of symptoms. The clinical diagnosis was idiopathic aplastic anemia. At *autopsy*, the marrow removed from the femur, rib and vertebra was extremely cellular. There were many groups of developing erythrocytes, both early and late. Myelocytes were abundant in various stages of growth. Megakaryocytes were present in normal or slightly reduced numbers. There was no evidence of leukemia. Examination of the other organs showed no anatomic basis for the hypocythemia.

CASE 6 (No. 303995).—A red-headed Irish boy, aged 25, who came in with a 6 months' history of progressive weakness and pallor, had had no loss of weight, but occasional nose bleeds and occasional purpuric spots. Examination showed many small purpuric spots. There was no enlargement of the spleen or lymph nodes. Tourniquet test was positive. R. B. C., 2,000,000; Hgb., 40 per cent; W. B. C., 1700; Pmn., 19 per cent; platelets, 14,000. There was moderate variation in size and shape of the red cells with occasional normoblasts at all times. Reticulocytes varied from 1.4 to 6.3 per cent. Young neutrophils and occasional myelocytes were present throughout. In spite of many transfusions, large amounts of liver, nucleotide, ventriculin and iron, the course was progressive and the patient died 14 months after the onset of symptoms. At *autopsy*, the marrow from the femur and rib was definitely hypoplastic, the normal cellular elements being largely replaced by a mass of plasma cells and lymphocytes. Except for an old, scarred duodenal ulcer, examination of the other organs showed no anatomic basis for the hypocythemia.

CASE 7 (No. 328957).—An American man, aged 41, was admitted with a 2 months' history of increasing weakness and pallor. He had had several profuse nose bleeds and occasional ecchymoses. On admission the tourniquet test was found to be negative. There were many small purpuric spots and petechiæ. The spleen was just palpable. R. B. C., 2,900,000; Hgb., 45 per cent; W. B. C., 3100; Pmn., 12 per cent; platelets, 21,000. There was moderate variation in size and shape of the red cells. Nucleated red cells appeared in 1 to 5 per hundred W. B. C. Reticulocytes, 0.7 per cent. In spite of the low granulocyte count, there was a gradually increasing number of myelocytes and myeloblasts until shortly before death, when 35 per cent of the white cells were myeloblasts. In spite of 4 transfusions, intramuscular nucleotide, large amounts of parenteral liver extract

and iron, the course was progressive and the patient died 4 months after the onset of symptoms. Because of a large number of embryonic white cells the final clinical diagnosis was acute aleukemic myeloid leukemia. At *autopsy*, marrow from the femur was aplastic with much fat and only occasional small islands of developing cells. There were, however, many islands of extramedullary blood formation in the liver, spleen and lymph nodes. There was no evidence of leukemia. Examination of the other organs revealed no anatomic basis for the hypocythemia.

CASE 8 (No. 339588).—An American man, aged 61, who was admitted with a 4 months' history of progressive weakness and pallor. On admission he was critically ill with a high fever and evidence of pneumonia in both lungs. No petechiae or purpuric spots. There was a large sloughing ulcer of the palate. The spleen could not be felt. R. B. C., 1,400,000; Hgb., 30 per cent; W. B. C., 150; Pmn., 16 per cent; platelets markedly decreased. Reticulocytes were not counted. There was marked variation in size and shape of the red cells and much basophilic stippling. There were many nucleated red cells and occasional megaloblasts. Myelocytes were present in small numbers. He was given 2 transfusions, but died the 2d day. The final diagnosis was idiopathic aplastic anemia and terminal pneumonia. At *autopsy*, marrow removed from the femur, rib and vertebra was extremely hyperplastic, containing large numbers of young cells, both of the red and white series, in all stages of development, and a normal number of megakaryocytes. Examination of the other organs showed nothing of note except a bilateral confluent bronchopneumonia.

CASE 9 (No. 352884).—An American man, aged 59, was admitted with an 8 months' history of progressive weakness, pallor and loss of 62 pounds in weight. For 2 years, ending 1.5 years before the onset of symptoms, he had been in daily contact with benzol fumes. There had been no purpura. The spleen was not enlarged. R. B. C., 1,400,000; Hgb., 30 per cent; W. B. C., 750; Pmn., 4 per cent; platelets, 36,000; reticulocytes, 0.1 to 1.4 per cent. There was moderate variation in size and shape of red cells and rare normoblasts were found in all the sinuses. Occasional myelocytes and rare myeloblasts were seen. In spite of transfusions, parenteral liver extract and a high vitamin diet, the patient failed rapidly and died 8.5 months after the onset of symptoms. It was of interest that although a carious tooth was extracted when the total white cell count was below 500 no ulceration appeared. The final diagnosis was "aplastic" anemia, possibly secondary to exposure to benzol. A sternal puncture was done 8 days before death, which showed an extremely active, cellular marrow with many young cells of all types in all stages of development. At *autopsy*, marrow removed from the femur, rib and vertebra was distinctly less cellular than the marrow of the sternum, but contained an apparently normal number of young red cells and white cells, as well as a definitely increased number of megakaryocytes. Examination of the other organs showed no anatomic basis for the hypocythemia.

CASE 10 (No. 364427).—An American man, aged 53, who came in with a 2 years' history of progressive weakness and pallor. For several months immediately preceding the onset of symptoms he had been exposed to large amounts of benzol fumes while working in an unventilated photographic dark room. The present illness began with a nose bleed which was shortly followed by purpuric spots and progressive pallor. On admission the spleen was enlarged, reaching 2 cm. below the costal margin. There was no enlargement of the lymph nodes. R. B. C., 2,400,000; Hgb., 55 per cent; W. B. C., 1800; Pmn., 52 per cent; platelets, 18,000; reticulocytes, 18 per cent. Normoblasts 1 to 10 per hundred W. B. C. There was moderate variation in size and shape of the red cells with marked basophilic stippling. The white cells showed a shift to the left, with occasional myel-

ocytes and rare myeloblasts. In spite of transfusions, parenteral liver extract, large amounts of iron and nucleotide, he failed rapidly. He developed bilateral bronchopneumonia and died shortly after admission. The final diagnosis was "aplastic" anemia due to benzol poisoning, bronchopneumonia, terminal hemolytic streptococcus bacteremia. At *autopsy*, the marrow removed from the sternum, rib, femur and vertebra was the same in all instances and consisted of a mass of early myelocytes and erythroblasts. The myelocytic hyperplasia of the marrow was almost as extensive as that seen in chronic myeloid leukemia. There was no evidence of leukemia elsewhere in the body. The spleen weighed 370 grams and contained, as did the liver, scattered islands of blood formation. There was a terminal pneumonia and a very recent implantation of streptococci on the tricuspid valve. This case illustrates, apparently, the extreme myeloid activity that may occur as a late result of bone marrow injury.\*

CASE 11 (No. 350651).—A German Jew, aged 58, was admitted with a 2 months' history of progressive weakness and pallor. There had been no loss of weight. The spleen was enlarged to 2 cm. below the costal margin. R. B. C., 1,600,000; Hgb., 33 per cent; W. B. C., 800; Pmn., 16 per cent; platelets, 1800; reticulocytes, 5.2 per cent. Nucleated red cells 2 to 5 per hundred W. B. C. There was moderate variation in size and shape of the red cells. Myelocytes and myeloblasts appeared up to 10 per cent of the white cells. In spite of transfusions, parenteral liver, nucleotide, various vitamins and iron, the patient failed and died 5 months after the onset of symptoms. *Biopsy*: Permission for autopsy was not granted, but antemortem removal of a specimen of marrow from the sternum revealed almost complete aplasia of the marrow elements with replacement by connective tissue and fat.

CASE 12 (No. 356328).—A young Norwegian, aged 27, who came into the hospital with a 12 months' history of progressive weakness and pallor. There was no enlargement of the spleen and lymph nodes, no loss of weight, and no petechiæ. R. B. C., 1,000,000; Hgb., 22 per cent; W. B. C., 1150; Pmn., 24 per cent; platelets, 20,000; reticulocytes, 3.3 per cent. There was moderate variation in size and shape of the red cells and occasional normoblasts were seen. There was again a shift to the left in the white cells and occasional myelocytes appeared in all preparations. *Biopsy*: Examination of the sternal bone marrow revealed a very cellular; extremely active marrow containing an increased number of all the normal elements, apparently in normal relative proportion. After several transfusions, the patient was discharged, at his request, to return to Norway. The final diagnosis was idiopathic "aplastic" anemia.

CASE 13 (No. 268399).—An American-born Jew, aged 31, with a 7 years' history of slowly progressive weakness and pallor. The spleen was just palpable. There had been no purpura. R. B. C., 730,000; Hgb., 14 per cent; W. B. C., 1700; Pmn., 28 per cent; platelets, 9000; reticulocytes, 3 per cent. There was moderate variation in size and shape of the red cells with rare myelocytes and young polymorphonuclears. During the 7 years that he had been ill, he had received a total of 68 transfusions. While in this hospital he was given large amounts of pentnucleotide and intramuscular liver extract without response. *Biopsy*: Marrow removed from the sternum showed mild hypoplasia with a slight decrease in the number of young cells, although a considerable number of formative elements remained.

**Analysis of Data.** The more important findings revealed as follows:

1. *Sex.* Of the 13 cases 12 were males.

\* This case will be published in detail by Dr. Dorothy H. Andersen.

2. *Age.* The youngest was 25 years of age, the oldest 70, and the average 46.

3. *Relevant Factors in the Past History.* In 2 of the 13, exposure to benzol fumes was definitely established. In Case 9 there had been an interval of 18 months between the last exposure and the first symptom. In Case 10 extensive exposure continued up to the clinical onset of the disease. In Case 3 excessive and prolonged exposure to Roentgen ray was thought to be of considerable etiologic importance. Nothing that could even remotely be considered as a relevant causal possibility was found in the other cases. A variety of nationalities and an assortment of occupations existed. There was no evidence of preliminary infection and no suggestion of familial occurrence.

4. *Symptoms.* In 10 of the 13 cases the disease began insidiously with weakness and pallor, in only 3 did purpuric manifestations signal the onset or appear during the course. The symptoms in all were the symptoms of progressive anemia.

5. *Physical Examination.* There was little or no evidence of loss of weight. The striking physical finding was the extreme pallor without the lemon-yellow tinge seen in the presence of increased red cell destruction. In 3 there were purpuric spots of various sizes, in 2 others occasional petechiæ were seen, in 8 there was no evidence of increased bleeding. In 2 the spleen was enlarged to 2 to 4 cm. below the costal margin, in 3 others it was just palpable at the end of inspiration, in 8 it could not be felt at any time.

6. *The Blood Picture.* The one outstanding feature of this group of cases was the progressive depletion of the number of formed elements in the peripheral blood.

(a) *The Red Blood Cells.* At the time of admission to the wards the number of red blood cells per c.mm. averaged 1,500,000. There was in the whole group surprisingly little variation from this number. Following transfusions transient rises in the red count occurred, but the degree, as well as the duration, of the response became less and less as time went on. The hemoglobin (corrected Sahli technique) averaged 20 per cent on admission, the color index remaining near 1 throughout.

(b) *The White Blood Cells.* There was a persistent leukopenia in all cases, the average admission white count being 1500 per c.mm., the highest 3100 and the lowest 150. In all there was a marked reduction in the percentage of neutrophils, the highest being 52 per cent, the lowest 4 per cent and the average 25 per cent.

(c) *Platelets.* With the exception of one platelet count of 77,000 per c.mm., all platelet counts in all cases were below 50,000.

(d) *Reticulocytes.* The percentage of reticulated red cells varied considerably, the lowest being 0.1 per cent and the highest 18 per cent. Variations occurred in the same individual with irregular changes from time to time. In the majority of cases, however, the reticulocytes were slightly to moderately increased.

(e) *The Blood Smears.* Wright stained coverslip preparations revealed changes quite different from the accepted aplastic anemia blood picture.

In all of the cases the red blood cells showed considerable to marked variations in size, in shape, in hemoglobin content and in staining reaction. There was no constant trend in the size of the cells, no definite tendency to macro- or microcytosis. The poikilocytosis was not as marked as in cases of pernicious anemia but was very definite. In all cases there was some polychromasia and in two the degree of basophilic stippling was extreme. In addition normoblasts were seen in all cases, varying from a relatively small number up to 8 to 10 per 100 W. B. C.

In spite of neutropenia, there was, in all cases, a definite shift to the left in the granulocytes. In all cases myelocytes were seen and in all but 3 myeloblasts were occasionally noted. In 3 cases the percentage of embryonic granulocytes reached sufficient proportions to warrant the consideration of acute leukemia as a possible final diagnosis.

(f) In 8 of the 13 cases there was no evidence of increased blood destruction and the urobilin excretion and serum bilirubin fell within normal limits. These determinations were not done in the remaining 5 cases.

7. *The Bone Marrow.* In sharp contrast to the uniform clinical and hematologic picture was the appearance of the bone marrow. In only 1 of the 13 cases was the marrow that was examined found to be aplastic. In 2 others there was moderate hypoplasia, in 3 the marrow appeared morphologically normal. In the remaining 7 the marrow was extremely cellular with marked increase in one or more of the developing cell types. In 3 of these 7 there was a general hyperplasia of all the elements, in 2 the hyperplasia was most apparent in erythroblastic activity, in 1 a marked increase in megakaryocytes was noted, in addition to an increase in red and white cell development, and in 1, a case of benzol poisoning, the marrow was filled with myelocytes in various stages of development. There was no postmortem evidence of leukemia in any case, nor was any anatomic basis for the condition found. Neither was there any reason for believing that any of these cases should have been considered as examples of pernicious anemia, thrombocytopenic purpura or agranulocytosis.

**Discussion.** There are several obvious, major discrepancies between aplastic anemia as it is usually described in the textbooks and "aplastic" anemia as we have seen it in this clinic. These discrepancies require explanation. Three possible explanations exist.

1. In the first place it is possible that, through some queer error in normal probability, there has not been a case of aplastic anemia in this hospital during the past 15 years. If the clinical diagnosis of aplastic anemia is rigidly limited to the usual specifications all of the above cases should have been given another name. If we

accept the absence of evidence of regeneration in the peripheral blood as an essential feature of typical aplastic anemia, if we require for diagnosis a fulminating disease with high fever and rapid course, then the clinicians of this hospital erred. If aplasia of the bone marrow is the major requirement at autopsy, we have seen only 1 case of aplastic anemia from the pathologist's point of view and our pathologists have erred in calling any of the other 12 cases "aplastic." If, on the other hand, progressive hypocythemia is the only requirement, all of the above cases meet that requirement and our diagnoses are sustained. In other words the clinical and anatomic diagnosis depends entirely upon one's definition of the syndrome, and a statement of the requirements and restrictions that must be met.

2. In the second place, it is possible that the requirements for diagnosis as set forth in various textbooks and reviews may not be entirely supported by the available clinical evidence. With this possibility in mind, examination of the literature revealed several points of interest.

The first case of "aplastic" anemia on record and the one most frequently referred to is that of Ehrlich.<sup>1</sup> The clinical and hematologic data are meager and questionable (the red count is reported as 213,000, a white count was not done, the platelets are not mentioned, the tibial marrow appeared yellow and fatty). Following this publication there appeared, from time to time, case reports of patients presenting similar pictures. By 1908 Cabot<sup>2</sup> was able to collect 24 cases and Hirshfeld,<sup>3</sup> in 1911, found the total to be 44. Musser<sup>4</sup> reviewed the situation up to 1914. In 1919, in a careful survey of the subject, Smith<sup>5</sup> collected and analyzed 64 cases of aplastic anemia. Although he appreciated the incompleteness of many of the recorded cases, he felt that the disease was uniform and readily recognizable, that it occurred chiefly in young adults (average age 29.5 years), that it progressed rapidly (average duration 3 months) and that it was characterized by a progressive decrease in the number of formed elements in the blood. There was an absolute lack of all young forms and the marrow was fatty in all cases. The conclusions arrived at by Smith express the opinions of the previous authors. For the most comprehensive recent reviews, the articles by Root<sup>6</sup> and Carey and Taylor<sup>7</sup> may be consulted. The latter authors find the 1931 total of reported cases reaching 150.

Perusal of these reviews would tend to convince one that idiopathic aplastic anemia is a uniformly acute, rapidly fatal disease of adolescents and young adults, that it is associated with a high fever, a rapid decrease in the cells of the blood, that there is never any suggestion of regeneration of these blood cells and that "at necropsy the marrow shows practically complete fatty degeneration."<sup>8</sup>

If, however, the individual case reports on which the reviews are

based are examined, the clinical, hematologic and pathologic findings do not always conform to the expressed requirements. Many of these reviews include cases so inadequately studied as to render them useless for analysis. Adequate blood counts may be lacking, often there is no description of the blood smears and, in a surprisingly large number, there was no microscopic examination of the bone marrow. In addition cases are included that, on closer examination, present definite variations from the accepted and stated standards, cases in which evidence of regeneration was present, cases in which the marrow was not fatty.

If analysis is restricted to those case reports that are complete and detailed, three variants of "aplastic" anemia become apparent. It is obvious that cases occur that conform, in all respects, to the accepted picture. If the cases of, for example, Muir,<sup>9</sup> Lavenson<sup>10</sup> and Smith<sup>5</sup> are examined, it is obvious that there is, without question, a disease of young people, acute and fulminating in its course, with a rapid decrease in the cellular elements of the blood, without evidence of regeneration, and with a complete aplasia of the marrow at necropsy. In addition, there is a second group comprising a few cases whose clinical features are similar to the preceding group, but in which the marrow, instead of being fatty, was found to have a normal or even increased cellular content. Such cases have been reported by Naegeli,<sup>11</sup> Senator,<sup>12</sup> Wolff<sup>13</sup> and Root<sup>6</sup> and several appear in the Italian literature<sup>14,15,16</sup> under the name of "pseudo-aplastic" anemia, a term suggested by Luzzatto<sup>15</sup> to indicate the discrepancy between the blood and bone marrow picture. The third variation comprises cases of progressive hypocythemia in which evidence of regeneration appeared in the peripheral blood, such as in the detailed reports of Blumer,<sup>17</sup> Sabrazes, Micheleau and Mandillon,<sup>18</sup> Di Guglielmo (1928), Merklen and Wolf,<sup>23</sup> and the cases observed by us. In some of these cases (all but one of ours) the marrow was found to be cellular, so that the question is raised as to whether this condition of the marrow could not have been diagnosed correctly from examination of the blood. However, in the 1 case in our series in which the marrow of the sternum was aplastic, immature cells appeared in the circulation in numbers as great as in the other 12 cases, apparently coming from extramedullary foci or from hyperplastic foci in the marrow of bones not examined. Also, in Di Guglielmo's cases (1928) it was found that immature red and white cells appeared with fatty marrow. This author lays particular emphasis on the occurrence of immature cells, and states that the essential character of the disease, from the hematologic standpoint, "is not the absolute absence of erythroblasts during the whole course, but the irreducible and progressive diminution of the number of the morphological elements of the blood"—a feature which we also consider essential, and to which we have referred as "progressive hypocythemia."



It is extremely difficult to obtain a clear idea of the clinical, hematologic and pathologic pictures of the disease in the majority of these case reports. In a great many of the older records confusion with pernicious anemia exists. Reticulocyte counts, leukocyte "shifts," platelet counts, were not a part of the routine technique and adequate marrow preparations are lacking. But from even such a brief presentation of the acceptable records it would seem that the diagnosis of aplastic anemia had been stretched at times so as to include fairly obvious variations from the previously accepted standards.

3. A third possible explanation of the discrepancies existing within our group, and between our cases and the accepted descriptions, exists. It would seem possible to have a progressive decrease in the number of circulating blood elements as a result of a variety of causal agents acting on the marrow; that although the peripheral blood pictures might be in many ways similar, the terminal microscopic appearance of the marrow might vary with the nature of the disturbing agent, with the type of injury sustained, with the degree of regeneration permitted, with the piece of marrow examined or even the time of examination. Some such explanation would seem to be the most compatible with the evidence at hand.

There is no question but that progressive hypocythemia may be secondary to various marrow toxic agents, the most widely studied of these being benzol. It is now known that the morphologic appearance of bone marrow previously injured with this chemical is far from uniform. In most animal experiments and in most human cases, chronic benzol poisoning results in aplasia of the marrow. But in some experimental animals<sup>19</sup> and in some human cases (such as Dr. Cabot's case report,<sup>20</sup> the case of Martland quoted by Hamilton<sup>24</sup> and Case 10 in our group) the marrow was found to be hyperplastic and it is important that in these, as well as the typical "aplastic" instances of benzol poisoning, the blood picture was that of progressive hypocythemia. What we seem to be dealing with in all is a severe disturbance in bone marrow function that may not invariably be correlated with bone marrow morphology. The peripheral results of the injury may be the same, but the visible effects on the marrow at the time of removal may be quite different.

This discrepancy between the functional activity of the marrow and the morphology of a minute fragment is seen in various other conditions. As examples: it is not uncommon to find a persistent leukopenia in cases of leukemia; the marrows of patients dying of agranulocytosis may appear normal or even hyperplastic as far as the granulocytic elements are concerned (Fitzhugh and Krumbhaar<sup>21</sup>); in pernicious anemia there is extreme hyperplasia of primitive red cells, and in many of the recorded examples of "gelatinous

degeneration" of the marrow the blood counts have been within normal limits.

Another difficulty appears when it is realized that the appearance of a fragment of marrow may be no indication of the state of this organ elsewhere in the body. That marked variation in cellularity may occur within a radius of a few millimeters is generally appreciated and has been thoroughly discussed by others.<sup>22,23</sup>

It would seem, therefore, that examination of the peripheral blood may be no index as to the morphologic appearance of the fragments of marrow examined and that the morphologic appearance of the marrow may be no index as to its functional activity.

**Summary and Conclusion.** 1. Thirteen cases of "aplastic" anemia have been studied. In all, the disease was characterized clinically by a progressive decrease in the number of erythrocytes, leukocytes and platelets—a progressive hypocythemia. In all, evidences of attempted regeneration were noted in the peripheral blood.

2. The marrow revealed a wide variation in microscopic appearance. In only 1 of the 13 was the marrow aplastic. In 2 it appeared hypoplastic, in 2 it was morphologically normal. In the remaining 8 there was moderate to marked hyperplasia of one or more of the formative elements.

3. It is felt that many of the restrictions and limitations placed on the clinical and pathologic diagnosis of "aplastic" anemia should be removed and that progressive hypocythemia alone should be sufficient reason for making the diagnosis, provided leukemia can be excluded.

4. The lack of correlation between the blood picture and bone marrow morphology has been discussed. It is felt that examination of the peripheral blood may be, at times, no index as to the condition of the blood-forming apparatus. Specifically, progressive hypocythemia as observed in these cases is not, in itself, sufficient evidence on which to postulate the presence of aplastic bone marrow.

5. This strongly suggests that it is quite possible to have serious interference with the normal processes of development, maturation and delivery of blood cells without evident alteration in the cellular content of the marrow.\*

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\* While accepting the probable correctness of the authors' thesis, it would seem as if the situation would be clarified by using for the present, at least different labels for the 3 varieties; thus, "aplastic anemia" might be reserved as many now do, for the type without evidence of regeneration in blood or bone marrow; "pseudo-aplastic anemia" for the variety with cellular bone marrow; and "progressive hypocythemia" for the kind here described, *i. e.*, with evidences of attempted regeneration in both blood and bone marrow.—EDITOR.

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## THE BLOOD CYTOLOGY IN UNTREATED AND TREATED SYPHILIS.

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IMPROVED methods for the study and differentiation of living cells based on physiologic activity has provided means for investigating blood and tissue reactions from a functional as well as a morphologic point of view. These methods have been applied to the study of syphilitic reactions in man<sup>1</sup> and animals.<sup>2</sup> The present report is concerned with the blood cytology, as determined by the supravital technique, of patients with untreated and with treated syphilis. A subsequent paper will discuss the blood cytology in the active and latent stages of the experimental disease.

**Material and Methods.** Observations were made on the blood cytology of 213 syphilitic patients.\* Of these, 87 had received no treatment, and 126 had been variously treated before the blood examinations were made. The untreated group was composed of 48 patients with active primary infection, 23 patients who had active secondary lesions, and 16 who presented signs and symptoms of tertiary disease. The treated group consisted of 43 patients on whom treatment was started in the primary stage, 30 who had received their first treatment in the secondary stage, and 53 who began their treatment in the tertiary phase. The clinical diagnosis

\* Through the kindness of Dr. Howard Fox, these patients were made available for study in the Syphilis Clinic of the University and Bellevue Hospital Medical College, New York University.

of syphilis was confirmed in all cases by dark-field or serologic examination. This report is essentially limited to the study of white males. Of the 213 patients, 29 were colored and 7 were females.

The blood examinations were conducted from November, 1930 to November, 1932; with the exception of March, 1931, and July, August and September of 1931 and 1932, counts were made every month during this interval. Since the patients were ambulatory and repeated counts could not readily be obtained, only one complete blood examination was made on each individual. Each examination included a total white and red cell count made with standardized automatic pipettes, a platelet count by the Ringer-heparin method of Casey,<sup>3</sup> a hemoglobin determination by the Newcomer method, and a differential white cell count, using the supravital neutral red technique, 100 cells being counted on each of two smears. The blood samples were taken in the afternoon, usually between 2.00 and 3.00 P.M., and examined later<sup>4</sup> the same afternoon. From 2 to 7 blood examinations were made on those afternoons devoted to this study. One observer made all the red cell, white cell, platelet and hemoglobin determinations, and all the differential smears were examined by the same two observers.

Most of the treated patients received alternating doses of neoarsphenamin and mercury, but many had been treated either entirely or at some time with various drugs, including bismuth, arsphenamin, sulpharsphenamin, silver arsphenamin and tryparsamid. The amount of treatment ranged from less than one course to several courses separated by rest periods. Classification on the basis of the drugs used, the dose and frequency of administration has not been attempted.

In the analysis of the results, the usual statistical methods were employed for determining the mean, the standard error of the mean, and the standard error of the difference of two means. A difference was considered significant when the probability of its occurrence by chance was less than one in 100 ( $t = 2.5$ ,  $P = 0.01$ ). The  $\chi^2$  method is that described by Fischer.<sup>5</sup>

It is usual in a study of the blood picture in any disease to indicate whether the findings are higher, lower, or the equivalent of normal values. In the present study there were two objections to this procedure. The normal limits of variation in the number of white blood cells in man is usually given as ranging between 5000 and 10,000, with an average of 7500. In our experience of weekly counts on a small group of normal young men over a period of 2 years,<sup>6</sup> the mean total white cell count was nearer 6500 than 7500. In addition to this discrepancy between accepted values and our own for the total white cell count, a second difficulty was the fact that, so far as is known, there has not yet appeared an adequate statistical survey of the differential cell formula of normal individuals as determined by the neutral red supravital technique, the method employed in this study. Because of these two facts, we have hesi-

tated to ascribe normality to any of the values obtained in this investigation.

We have, however, made an effort to determine the differences, if any existed, between the supravital and fixed smear methods in our hands. Duplicate counts were made on the first 86 patients of this series with the two techniques. The cover-slip method was employed in the preparation of the fixed smears, and 100 cells were counted on each of two smears after staining by Wright's method. A comparison of the mean values for the counts on these 86 individuals revealed that significant differences were present. Counts made with the supravital technique gave significantly higher values for neutrophils, basophils, and monocytes, and a significantly lower value for lymphocytes, than did duplicate counts on fixed smears. The eosinophils were slightly higher with the neutral red method, but this difference was not significant. (Neutrophils: Difference,  $2.4 \pm 0.97$  per cent;  $t$ , 2.5;  $P$ , 0.01. Basophils: Difference,  $0.3 \pm 0.10$  per cent;  $t$ , 3.0;  $P$ , 0.01. Monocytes: Difference,  $1.7 \pm 0.53$  per cent;  $t$ , 3.2;  $P$ , 0.01. Lymphocytes: Difference,  $4.7 \pm 0.89$  per cent;  $t$ , 5.3;  $P$ , 0.01. Eosinophils: Difference,  $0.3 \pm 0.29$  per cent;  $t$ , 1.1;  $P$ , 0.2.) With the exception of the findings for monocytes, the direction of these differences was similar to that observed by Sabin.<sup>7</sup>

Since comparisons with normal values could not be made, the procedure adopted was to group the patients in a systematic manner, and compare the blood cell values of one group with those of another. In this way errors which might be due to variations in technique, in observers, and countries are minimized.

**Results.** The essential findings are summarized in Tables 1 to 7. The values given in Tables 1 and 2 are represented graphically in Figure 1.

*The Blood Cytology in Untreated Syphilis.* The mean blood cell values of the untreated patients whose blood was examined in the primary, secondary or tertiary stages are shown in Table 1. No significant differences were found between any of the blood elements of the primary and secondary cases. The comparative infrequency of untreated tertiary syphilis is evidenced by the small number of individuals in this group. There were a sufficient number of observations, however, to show that the mean monocyte count was significantly lower than that for both the primary and secondary cases. (Primary: Difference,  $297.8 \pm 97.3$ ;  $t$ , 3.06;  $P$ , 0.01. Secondary: Difference,  $425.3 \pm 115.7$ ;  $t$ , 3.67;  $P$ , 0.01.) Of interest also is the low mean value for the red cell count in the tertiary group. This was significantly lower than the red cell count in the primary syphilitics, and probably significantly lower than the mean red cell count of the patients with secondary disease. (Primary: Difference,  $437,000 \pm 14,500$ ;  $t$ , 3.01;  $P$ , 0.1. Secondary: Difference,  $358,000 \pm 17,300$ ;  $t$ , 2.06;  $P$ , 0.05.) It will be noted that although

the differences were not statistically significant, the values for the total white cell count, platelet count and neutrophils were lower in tertiary syphilis, while the lymphocytes were higher than in either of the early stages. These differences no doubt would have been of greater significance had the number of patients

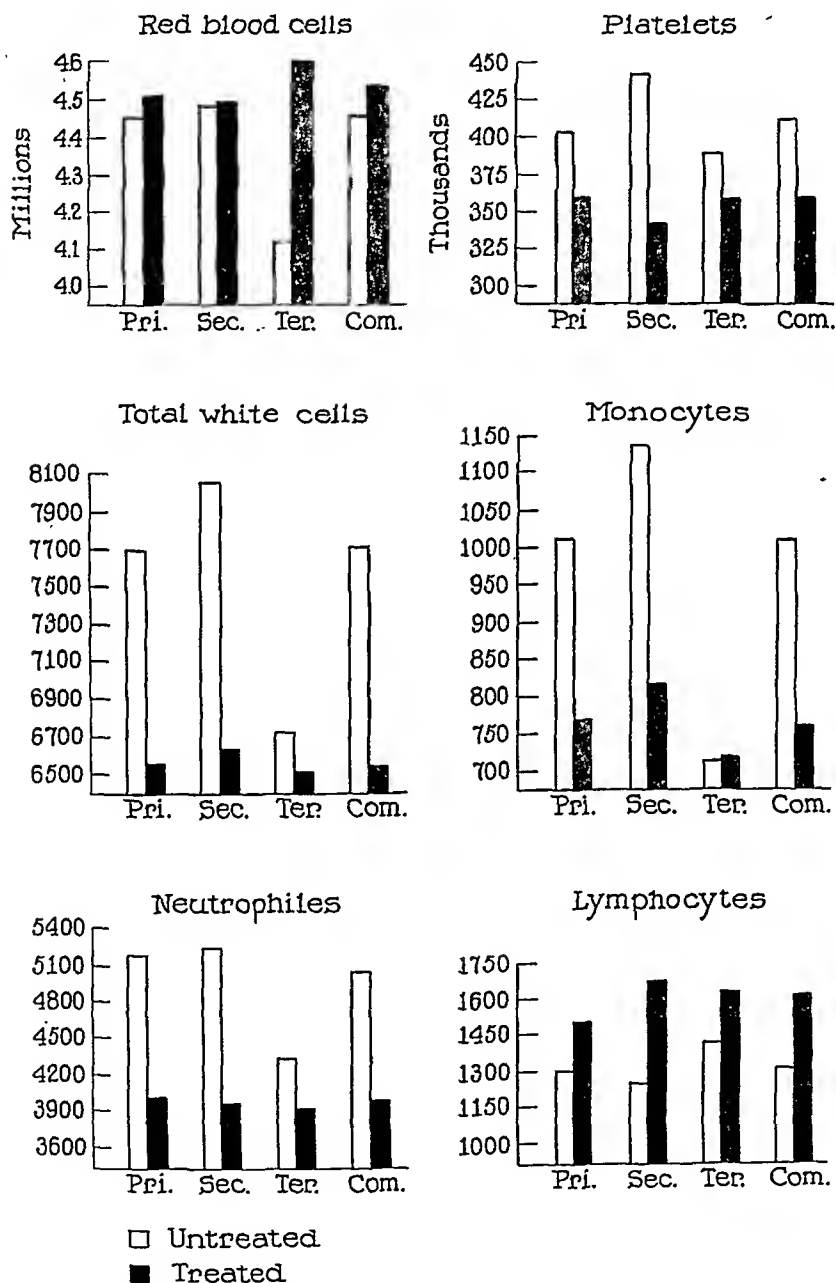


FIG. 1.—The blood cytology in untreated and treated syphilis. Pri., Sec., and Ter. refer to the Primary, Secondary and Tertiary stage. Com. indicates the combined values for all three stages.

in the tertiary group been larger. A comparison of the findings in late syphilis (tertiary stage) with the combined values for early syphilis (primary and secondary stages), gave two highly significant differences. In the late group of cases both the red cell count and the monocyte count were significantly lower than the corresponding values for the early syphilis group. (Red cells—combined primary and secondary group:  $n$ , 71; tertiary group:  $n$ , 16. Mean<sub>n</sub>, 4,530,600  $\pm$  6,580. Mean<sub>n</sub>, 4,119,000  $\pm$  12,240. Difference, 411,600  $\pm$  13,900;  $t$ , 2.96;  $P$ , 0.01. Monocytes—Mean<sub>n</sub>, 1,051  $\pm$  49. Mean<sub>n</sub>, 712  $\pm$  77. Difference, 339  $\pm$  91;  $t$ , 3.71;  $P$ , 0.01.) On the same basis none of the other blood elements showed any statistically significant differences.

TABLE 1.—THE MEAN AND STANDARD ERROR OF THE MEAN OF THE BLOOD CONSTITUENTS IN UNTREATED SYPHILIS.

Stage.	No.	Value.	R. B. C.	H.	P.	W. B. C.	N.	B.	E.	L.	M.
Primary	48	Mean	+000 4456	% 69.0	+000 403	7696	5187	37	155	1306	1010
		Standard error of mean	$\pm 77.1$	$\pm 1.3$	$\pm 5.2$	$\pm 278.8$	$\pm 233.6$	$\pm 8.3$	$\pm 21.0$	$\pm 40.7$	$\pm 59.9$
Secondary	23	Mean	4477	63.8	441	8052	5247	63	323	1277	1137
		Standard error of mean	$\pm 123.5$	$\pm 1.8$	$\pm 25.7$	$\pm 529.1$	$\pm 377.5$	$\pm 13.4$	$\pm 82.8$	$\pm 113.6$	$\pm 86.7$
Tertiary	16	Mean	4119	65.5	389	6716	4355	62	184	1409	712
		Standard error of mean	$\pm 122.5$	$\pm 1.7$	$\pm 22.3$	$\pm 442.9$	$\pm 365.4$	$\pm 11.8$	$\pm 36.7$	$\pm 115.9$	$\pm 76.8$
Total	87	Mean	4455	67.0	411	7610	5050	48	205	1316	989
		Standard error of mean	$\pm 60.7$	$\pm 1.0$	$\pm 9.4$	$\pm 228.7$	$\pm 179.9$	$\pm 6.5$	$\pm 26.7$	$\pm 51.0$	$\pm 45.0$

R. B. C., red blood cell count; W. B. C., white blood cell count; P., platelet count; H., hemoglobin; N., neutrophils; B., basophils; E., eosinophils; L., lymphocytes; M., monocytes.

*The Blood Cytology in Treated Syphilis* (Table 2). Three subdivisions were employed in the analysis of these results, depending on whether treatment was begun in the primary, secondary or tertiary stage of the disease. No significant differences were observed in the blood formulæ of the three groups.

*Comparison of the Results for Treated and Untreated Syphilis.* The differences in the untreated and treated groups (Tables 1 and 2) were submitted to a further analysis. The mean values for the combined untreated group of 87 patients were compared with those of the combined treated group of 126 patients. In the treated group, the total white cell count was lower, the platelet count was lower, the hemoglobin in per cent was higher, the absolute number of lymphocytes was higher, and the absolute number of neutrophils and of monocytes was lower, than the corresponding values for the

untreated group. (Total white cells—Difference,  $1,051 \pm 275$ ;  $t$ , 3.8;  $P$ , 0.01. Platelets—Difference,  $53,000 \pm 11,000$ ;  $t$ , 4.7;  $P$ , 0.01. Hemoglobin—Difference,  $5.3 \pm 1.10$  per cent;  $t$ , 3.6;  $P$ , 0.01. Neutrophils—Difference,  $1,084 \pm 210$ ;  $t$ , 5.2;  $P$ , 0.01. Lymphocytes—Difference,  $290 \pm 69$ ;  $t$ , 4.2;  $P$ , 0.01. Monocytes—Difference,  $228 \pm 51$ ;  $t$ , 4.5;  $P$ , 0.01.) No difference was observed between the two groups with respect to the red cell count or the absolute numbers of eosinophils and basophils.

TABLE 2.—THE MEAN AND STANDARD ERROR OF THE MEAN OF THE BLOOD CONSTITUENTS IN TREATED SYPHILIS.

Stage.	No.	Value.	R. B. C.	H.	P.	W. B. C.	N.	B.	E.	L.	M.
Primary	43	Mean	$\frac{+000}{4511}$	$\frac{\%}{72.5}$	$\frac{+000}{358}$	6563	4039	59	192	1502	771
		Standard error of mean	$\pm 90.0$	$\pm 1.1$	$\pm 11.5$	$\pm 238.2$	$\pm 179.9$	$\pm 9.8$	$\pm 29.2$	$\pm 74.9$	$\pm 39.2$
Secondary	30	Mean	4487	72.9	341	6632	3941	46	147	1677	821
		Standard error of mean	$\pm 104.9$	$\pm 1.9$	$\pm 18.3$	$\pm 318.6$	$\pm 228.3$	$\pm 9.8$	$\pm 23.0$	$\pm 124.4$	$\pm 52.7$
Tertiary	53	Mean	4599	71.6	358	6511	3921	50	172	1650	718
		Standard error of mean	$\pm 104.9$	$\pm 1.5$	$\pm 9.9$	$\pm 254.9$	$\pm 171.2$	$\pm 13.5$	$\pm 17.3$	$\pm 59.5$	$\pm 37.0$
Total	126	Mean	4542	72.3	358	6559	3966	52	174	1606	761
		Standard error of mean	$\pm 53.8$	$\pm 0.8$	$\pm 6.2$	$\pm 153.2$	$\pm 107.6$	$\pm 6.2$	$\pm 13.3$	$\pm 46.5$	$\pm 24.1$

R. B. C., red blood cell count; W. B. C., white blood cell count; P., platelet count; H., hemoglobin; N., neutrophils; B., basophils; E., eosinophils; L., lymphocytes; M., monocytes. The designations, *primary*, *secondary* and *tertiary*, refer to the stage in which treatment was begun.

In relative percent the same differences were noted between the white cell formulæ of the treated and untreated groups as for the absolute numbers of the white cell components (Table 3). It will be seen that the neutrophils and monocytes of the treated group were lower, and the lymphocytes higher, than the corresponding cells in the untreated group.

TABLE 3.—MEAN BLOOD CELL VALUES IN PER CENT IN 87 CASES OF UNTREATED AND 126 CASES OF TREATED SYPHILIS.

	Neutrophils.		Basophils.		Eosinophils.		Lymphocytes.		Monocytes.	
	Untr.	Tr.	Untr.	Tr.	Untr.	Tr.	Untr.	Tr.	Untr.	Tr.
	%	%	%	%	%	%	%	%	%	%
Mean	65.6	59.8	0.6	0.7	2.7	2.6	17.9	24.9	13.1	11.7
Standard error of mean	$\pm 0.84$	$\pm 0.77$	$\pm 0.02$	$\pm 0.02$	$\pm 0.25$	$\pm 0.26$	$\pm 0.65$	$\pm 0.64$	$\pm 0.45$	$\pm 0.32$
Difference between means	$5.8 \pm 1.13$		$0.1 \pm 0.11$		$0.1 \pm 0.36$		$7.0 \pm 0.91$		$1.4 \pm 0.55$	
$t$	5.2		0.9		0.3		7.7		2.6	
$P$	0.01		0.3		0.8		0.01		0.01	

Untr. = Untreated.

Tr. = Treated.



**Discussion.** Thus the mean cell values of the total treated group of 126 patients differed from those of the untreated group of 87 patients in the following respects: Lower total white cell count, platelet, neutrophil and monocyte counts, and higher values for lymphocytes and hemoglobin. There are certain factors in the material itself which might have influenced these differences. These will be discussed in order.

*Number of Observations.* One factor which might account for the observed differences is the disproportion between the numbers of patients in the treated and untreated groups. The untreated series had only 16 patients in the tertiary group, while the treated series contained 53 patients who received their first specific treatment in the tertiary stage (Tables 1 and 2). Could this bias account for the differences between the blood cells of treated and untreated cases? If tertiary cases are omitted from both groups, and a comparison is made between the 71 untreated patients with early syphilis (primary and secondary stages), and the 73 patients treated in the early period, the two groups are more nearly comparable as far as numbers are concerned than if the total treated and untreated groups are considered. But the same differences are apparent as were observed between the total treated and untreated groups (Table 4). The total white count, the platelet count, the neutrophil and monocyte counts in the 73 treated patients were lower, and the lymphocyte count and the hemoglobin in per cent were higher, than the same values for the 71 untreated patients. There was no difference between the red cell values or the numbers of basophils and eosinophils in the two groups. It is evident, therefore, that the disproportion in the number of observations in the two groups did not introduce sufficient bias to account for the differences.

*Age.* The observed differences were not associated with any differences in age. The mean age of the 87 untreated patients was  $32.7 \pm 1.37$  years, while the mean age of the 126 treated patients was  $36.2 \pm 0.94$  years. The difference of  $3.5 \pm 1.66$  is not of statistical significance since it is only 2.1 times the standard error of the difference.

*Sex, Color and Time of Counting.* Of the 213 patients examined, 96.7 per cent were males, and 86.4 per cent were white. A bias which might be introduced by sex and color is therefore not effective in the present series. Since all counts were made in the afternoon, time of the day is not a factor which can account for the differences.

*Duration of Infection.* It has been shown that the values for the total white cell count, platelets, neutrophils and monocytes of the untreated late syphilis group were lower, and the lymphocytes higher, than the corresponding values for untreated early syphilis. These differences were similar in direction and affected the same cells as the differences noted between the untreated and treated early syphilis groups. Thus the values for untreated late syphilis

TABLE 4.—MEAN BLOOD CELL VALUES IN 73 CASES OF UNTREATED SYPHILIS AND 71 CASES OF TREATED SYPHILIS. COMBINED VALUES FOR PRIMARY AND SECONDARY STAGE.

	Platelets.		Hemoglobin.		White blood cells.		Neutrophils.		Lymphocytes.		Monocytes.	
	Untr.	Tr.	Untr.	Tr.	Untr.	Tr.	Untr.	Tr.	Untr.	Tr.	Untr.	Tr.
Mean . . .	+000	+000	%	%	7812	6577	5206	3999	1296	1574	1051	792
Standard error of mean	±0.8	±10.1	±1.18	±0.69	±255.9	±190.6	±200.0	±138.9	±94.4	±67.8	±49.4	±31.6
Difference between means	65 ± 14.0		5.4 ± 1.37		1235 ± 319		1207 ± 243.4		278 ± 116.2		259 ± 58.7	
t	4.6		3.9		3.9		4.9		2.4		4.4	
P	0.01		0.01		0.01		0.01		0.015		0.01	

Untr. = Untreated.

Tr. = Treated.

and those for treated early syphilis differed in the same manner from the values for the untreated patients with early syphilis. It is evident therefore that the duration of the infection is a factor which affects changes in the blood cytology independent of treatment, since many years may elapse between the primary and secondary stages of infection and the occurrence of tertiary disease. On the same basis it is possible that the changes observed in the treated group as compared with the untreated group might have been influenced by spontaneous variations occurring during the period required for treatment, and that these differences might have developed regardless of the institution of treatment. With this possibility in mind, a further analysis of the results was made.

Of the patients whose first treatment was begun in the primary stage, all cases were selected in which from 1 to 6 months had elapsed between the time of the first evidence of infection and the time when the blood cytology was studied. This group of 19 treated primary cases was compared with the 47 untreated cases of primary infection. The same differences were observed between the mean blood cell values of these two groups as were found between the combined treated and untreated groups.

It is evident, therefore, that the observed differences between the treated and untreated groups were associated directly with the institution of anti-syphilitic measures. It is of interest to recall the somewhat similar observations of Hazen.<sup>8</sup> He found that, under treatment, either with mercury or salvarsan or a combination of the two drugs, cases of syphilis show a fall in the total white count and percentage of neutrophils, and a rise in the percentage of lymphocytes. Moreover, the administration of mercury to a group of non-syphilitics caused a slight fall in the total white count and in the relative neutrophil count, and a rise in the relative lymphocyte count. A fall in the number of platelets after treatment

has been observed by Mu,<sup>9</sup> while Cummer<sup>10</sup> and Eason<sup>11</sup> and others have commented on the anemia of tertiary syphilis.

*The Monocyte and Lymphocyte in Syphilis.* The monocyte-lymphocyte ratio, which has been suggested by Cunningham, Sabin and their coworkers as a prognostic aid in tuberculosis, is of especial interest in the present observations. The mean M/L index for the total untreated group of this study was 0.80, while the total treated group gave a significantly lower M/L index of 0.52. This difference was due to a significantly higher lymphocyte and a significantly lower monocyte level in the treated group. The occurrence of an M/L index of less than 0.55 in the treated group, or of more than 0.55 in the untreated group, was significantly more frequent than would be expected from random association ( $\chi^2 = 29.51$ ;  $n = 1$ ,  $P = 0.01$ ). Not only were differences noted between the M/L indices of the untreated and treated groups, but within the treated group also such differences were observed. Among the treated patients there were 20 individuals whose Wassermann was repeatedly negative after intensive treatment. The M/L index of this group was 0.34. The average M/L index of a group of 25 patients whose Wassermann reaction was positive on more than one occasion after prolonged treatment was 0.60. Thus there appeared to be a relationship between the numbers of lymphocytes and monocytes in the blood stream and activity of the disease on the one hand, and the efficacy of treatment as evidenced by the Wassermann reaction on the other. This relationship was investigated more precisely.

The group of 20 persistently treated patients with negative Wassermann reactions, and the group of 25 persistently treated

TABLE 5.—INTENSIVELY TREATED SYPHILIS CASES CLASSIFIED AS TO BLOOD SEROLOGY AND M/L RATIO. OBSERVED AND EXPECTED VALUES.

	Observed.			Expected.		
	Less than 0.45.	0.45 or more.	Total.	Less than 0.45.	0.45 or more.	Total.
Wassermann positive	4	21	25	10	15	25
Wassermann negative	14	6	20	8	12	20
Total	18	27	45	18	27	45

patients with positive Wassermann reactions were utilized for the analysis. These groups were classified in two ways: as Wassermann positive or negative, and as having an M/L index of less than 0.45, or 0.45 and above (Table 5). The observed deviations from expectation were clearly significant ( $\chi^2 = 13.50$ ;  $n = 1$ ,  $P = 0.01$ ). In other words there was a high positive correlation between Wassermann negativity and an M/L index lower than 0.45, and between Wassermann positivity and an M/L index higher than 0.45.

In a similar manner the lymphocytes and monocytes of the two groups were studied. Again the two groups of 20 and 25 treated

patients were classified in two ways: as Wassermann positive or negative, and as having a total lymphocyte count of less than 1350 or more than 1350 per cc. (Table 6). The observed findings were significantly independent of expectation ( $\chi^2 = 8.10$ ;  $n = 1$ ,  $P = 0.01$ ). Put in another form, lymphocyte values higher than 1350 were more frequently associated with negative serology, and lymphocyte values under 1350 were more often associated with positive serology than could be expected from chance association.

The persistently treated group was again divided in two ways: as Wassermann positive or negative, and as having monocyte values of less than 700 or more than 700 per cc. The observed and expected values are presented in Table 7. The association of negative serology with monocytes less than 700, and of positive serology with monocytes more than 700 per cc. was significantly more frequent than would be expected from random association ( $\chi^2 = 7.98$ ;  $n = 1$ ,  $P = 0.01$ ).

TABLE 6.—INTENSIVELY TREATED SYPHILIS CASES CLASSIFIED AS TO BLOOD SEROLOGY AND LYMPHOCYTES PER CC. OBSERVED AND EXPECTED VALUES.

	Observed.			Expected.		
	Less than 1350.	More than 1350.	Total.	Less than 1350.	More than 1350.	Total.
Wassermann positive	14	11	25	9.4	15.6	25
Wassermann negative	3	17	20	7.6	12.4	20
Total . . . . .	17	28	45	17.0	28.0	45

TABLE 7.—INTENSIVELY TREATED SYPHILIS CASES CLASSIFIED AS TO BLOOD SEROLOGY AND MONOCYTES PER CC. OBSERVED AND EXPECTED VALUES.

	Observed.			Expected.		
	Less than 700.	More than 700.	Total.	Less than 700.	More than 700.	Total.
Wassermann positive	7	18	25	11.7	13.3	25
Wassermann negative	14	6	20	9.3	10.7	20
Total . . . . .	21	24	45	21.0	24.0	45

*Comparison of the Blood Cytology in Human and Experimental Syphilis.* A study has been made of the blood cytology in the active and healed phases of experimental syphilis. It was found that certain differences existed between the mean blood cell values of rabbits with active syphilitic lesions and the values for normal control rabbits. In the syphilitic group the total white blood cells, the number of platelets, and the neutrophils and monocytes were significantly higher, while the lymphocytes were significantly lower than the corresponding values for normal animals. In the spontaneously healed or latent phase of the disease, when the rabbits presented no clinically demonstrable evidence of infection, the blood

cell values were not different from normal findings with two exceptions: the red blood cell count and the hemoglobin in per cent were lower.

These findings are of interest since they parallel so closely the observations on the human disease reported in this paper. In the human disease as has been stated, treatment causes a fall in the white blood cell count, platelet, neutrophil and monocyte counts, and a rise in the value for lymphocytes, from the findings in untreated patients. In the experimental disease, spontaneous regression without treatment is accompanied similarly by a fall in the white blood cell count, platelet count, neutrophil and monocyte counts, and a rise in the lymphocyte count.

Another parallelism, between the red cells and hemoglobin of the human and experimental disease, is also striking. With the exception of the red cells, all the blood elements of the untreated tertiary group showed the same changes from the findings in the untreated early syphilis group as were noted as a result of treatment. The marked depression of the red cells would seem to indicate that the prolonged infection affects them more severely than the other blood constituents. Similarly in the experimental disease, several months after inoculation when clinical signs of infection had disappeared spontaneously without treatment, the red cells and hemoglobin were significantly lower than normal values, although all the other cell elements had returned to normal levels. The only difference observed between the treated and untreated tertiary groups of humans were in the red cells and hemoglobin, both of which were significantly higher in the treated patients. (Red blood cell count — Difference,  $480,000 \pm 16,100$ ;  $t$ , 3.0;  $P$ , 0.01. Hemoglobin — Difference,  $6.1 \pm 2.26$  per cent;  $t$ , 2.7;  $P$ , 0.01.) Thus it would appear that specific treatment of the tertiary disease in the human causes a rise of the red cell count and hemoglobin value to higher levels, and it is quite probable that similar treatment of the experimental disease would do likewise.

**Conclusions.** It has been shown that the treatment of syphilis causes a fall in the total white cell and platelet counts, and the absolute and relative numbers of neutrophils and monocytes, and a rise in the absolute and relative numbers of lymphocytes from values observed in untreated syphilis. That these changes can occur without treatment is evidenced by the fact that changes similar in direction were observed in untreated tertiary syphilis as compared with untreated primary and secondary syphilis. Moreover the same differences were present between the values for treated as compared with untreated early syphilis. One may reasonably conclude that the institution of treatment facilitates the blood changes which occur without treatment if the disease progresses to the tertiary stage. Treatment however accomplishes one additional change in the blood picture, in that it is associated with a rise in the

red cell and hemoglobin levels from the low values found in untreated tertiary syphilis.

It has been found that an M/L index higher than 0.55 occurs more frequently in untreated syphilis, and an M/L index lower than 0.55 more frequently in treated cases than would be expected from random association. Moreover, a definite relationship has been found in persistently treated patients between the Wassermann reaction and the values for lymphocytes, monocytes, and the resulting M/L index. The use of the M/L index as a prognostic aid in evaluating the efficacy of treatment is suggested by these findings.

The parallelism in the blood cell changes that exist between the human and the experimental disease in the rabbit, is further evidence of the similarity between the pathologic processes in the two hosts, and lends additional weight to conclusions drawn from experimental syphilis as applied to the human disease.

**Summary.** From a study of the blood cytology of 126 treated and 87 untreated syphilis patients it was found that:

1. Treatment causes a fall in the total white cell count, the platelet count, and the relative and absolute numbers of neutrophils and monocytes, and a rise in the relative and absolute numbers of lymphocytes, and per cent hemoglobin, from values observed in the untreated cases.

2. No significant differences were noted between the mean blood cell values of the primary and secondary untreated patients.

3. A marked anemia was the outstanding feature of the blood cytology in the untreated tertiary disease. This anemia was absent in patients whose treatment was begun in the tertiary stage.

4. No differences in the blood cytology of treated patients were noted when treatment had been begun in the primary, secondary or tertiary stages of the disease.

5. A monocyte-lymphocyte ratio higher than 0.55 was more frequent among untreated patients, and a monocyte-lymphocyte ratio less than 0.55 was more frequent among treated patients, than would be expected from random association.

6. In a group of persistently treated patients, repeatedly negative serology was more frequently associated with a monocyte-lymphocyte ratio less than 0.45, with lymphocytes higher than 1350 per cc., and with monocytes less than 700 per cc.; and persistently positive serology was more frequently associated with a monocyte-lymphocyte ratio higher than 0.45, with lymphocytes lower than 1350 per cc., and with monocytes higher than 700 per cc. than would be expected from random association.

7. The changes observed in the cytology of the treated patients as compared with the untreated patients were similar in direction and affected the same cells as the changes observed in the spontaneously regressed experimental disease as compared with the

period of lesion activity. This similarity lends additional weight to deductions drawn from the experimental disease as applied to human syphilis.

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### INVOLVEMENT OF THE EIGHTH NERVE IN SYPHILIS, WITH SPECIAL REFERENCE TO THE RESULTS OF TREATMENT.

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ALEXANDER<sup>1</sup> reviewed, in 1929, the extensive literature concerning the diagnosis of syphilis of the 8th cranial nerve. The otologic findings most commonly recorded are: (1) A lowered upper tone limit; (2) loss of acuity for high tones, sometimes accompanied by a loss for middle or for all tones; (3) shortened bone conduction associated with "normal hearing," as first noted by Beek;<sup>2</sup> and (4) impaired vestibular responses. The hearing defects, with the exception of the 3d point, are the classical signs of all forms of nerve deafness. Wodak, Wanner and Rhese (quoted by Alexander) have disputed this point, since they found such shortened bone conduction as frequently in non-syphilitics as in patients with syphilis. If they are correct, then it would follow that a diagnosis of syphilis of the eighth nerve is usually based only upon the finding of a nerve type of deafness in a patient with syphilis.

Bearing this point always in mind, the authors have statistically analyzed audiometric and other records of the hearing of a group of individuals with syphilis. Attention has been focussed upon the question of the effect of antisypilitic treatment upon hearing.

*Material and Method.* The material which forms the basis of this study is composed of 286 individuals with a well established diagnosis of syphilis. Some of these were examined as a part of the routine work of the Otological Research Laboratory, the others were referred from the Syphilis Division of the Medical Clinic of The Johns Hopkins Hospital following complaints on the part of the patients of some hearing defect or symptoms of vestibular disturbance.

The material, therefore, is not a random sampling, so that it is not possible to consider our data as representative of the incidence of inner ear disease in syphilis in general, or of the relative frequency in its various types. Bunch's audiometric data<sup>3</sup> show that the loss of acuity for high tones found in those with syphilis is on the average the same as in a general population, considering age and sex. Ciocco<sup>4</sup> reported that the incidence and degree of high tone loss in patients with all types of syphilis and in those with syphilis of the central nervous system is in no way different from that in non-syphilitics.

The hearing of each patient was examined with a Western Electric Company 1-A audiometer, supplemented in most cases by Weber, Schwabach and Rinne tests with a c<sup>2</sup> (512 d. v.) tuning fork. A Struycken monochord was used for the upper limit determination. All cases have been excluded in which there was a serious middle ear lesion or in which it was clear that the hearing defect antedated the acquisition of syphilis. The vestibular examination was limited usually to a cold caloric stimulation.

In Table 1 is given the race and sex distribution of the individuals studied, grouped according to the type of syphilis, as diagnosed in the Syphilis Division of the Medical Clinic.

TABLE 1.—DISTRIBUTION OF MATERIAL BY TYPE OF SYPHILIS, RACE AND SEX.

Type of syphilis.	White.			Colored.			Grand total.
	Males.	Females.	Total.	Males.	Females.	Total.	
Early . . . . .	4	2	6	2	..	2	8
Late (excepting neuro-syphilis) . . . .	32	15	47	54	52	106	153
Neurosyphilis . . . .	61	21	82	19	3	22	104
Congenital . . . .	7	10	17	1	3	4	21
Total . . . . .	104	48	152	76	58	134	286

*Classification of the Audiograms.* The audiograms are assigned, according to the degree of hearing loss, into the groups described by Ciocco.<sup>4</sup> Typical examples of good hearing (I) and of the three degrees of high tone loss (II, III, IV) are shown in Fig. 1. On the basis of Ciocco's data on the distribution of these hearing groups,



by age and sex, in a general population our material is divided into 3 yet larger groups. These are: (1) "Normal" hearing, including all with good hearing (Group I) and all of those with high tone loss of a degree within the expected limits for their age and sex; (2) "excessive high tone loss," in which are included those with a loss for high tones greater than would be expected for their age and sex; and (3) "subnormal" hearing, which includes those showing also a loss for low and middle tones. The individuals in this group have an impairment of hearing for speech varying from slight difficulty to total deafness. When the hearing loss is different for the two ears, the poorer one has been used in allocating the case to a group. Table 2 shows the distribution on this basis.

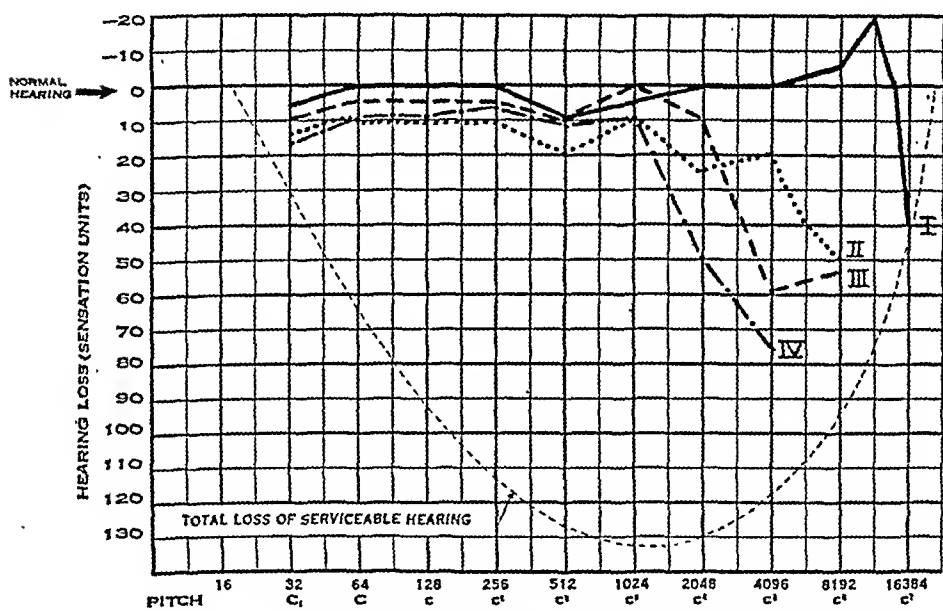


FIG. 1.—Representative audiograms of groups indicated. (From Ciocco, Laryngoscope, 1932.)

TABLE 2.—HEARING GROUP DISTRIBUTION ACCORDING TO AGE.

Age.	"Normal" hearing.	"Excessive high tone loss."	"Subnormal" hearing.	Total.
-20 . . . . .	7	1	4	12
20 to 29 . . . . .	29	12	10	51
30 to 39 . . . . .	37	24	16	77
40 to 49 . . . . .	48	25	8	81
50+ . . . . .	29	10	26	65
Total . . . . .	150	72	64	286

A high percentage of the individuals with "subnormal" hearing are above the age of 50 years. Analysis of the case histories involved has not provided an explanation for this. It is highly improbable that this represents an effect of age on hearing entirely independent of syphilis.

Reliable histories as to time and nature of onset of symptoms were obtained from 44 of the 64 patients in the "subnormal" hearing group; the onset was sudden in 20 and gradual in 24; it occurred before the beginning of treatment in 27 and after in 17. In these patients the hearing loss was unilateral in 16 and bilateral in 28.

*Bone Conduction.* We have regarded bone conduction time as shortened only in those cases in which, after repeated trials, it was consistently much less than the particular examiner's "normal." On this basis there are, of the 203 satisfactorily tested for this point, 58 with shortened bone conduction. These are distributed as follows: In the "normal" hearing group, 5 out of 92 tested; in the "excessive high tone loss" group, 7 among 53; and in the "subnormal" group, 46 out of the 46 giving reliable responses. A definitely disproportionate shortening of bone conduction is present in only a relatively small number of our cases. Of the 5 patients with "normal" hearing and shortened bone conduction, 3 are over 60 years of age and 2 over 40 years. The significance of this, in view of our method of classifying, is only that of a shortened bone conduction in a high tone loss.

*The Vestibular Reaction.* No attempt has been made to evaluate diminished reactions of a slight degree, these being included with the entirely normal ones and being termed "normal." Markedly reduced reactions, grossly sluggish responses and no reaction have been grouped together as "impaired." The vestibular test was done in 119 cases. It was found "normal" in 88 and "impaired" in 31. Since 21 of these latter are among the 40 "subnormal" hearing cases which had vestibular tests, it is evident that in syphilis the incidence of impaired vestibular function is greater when there is a marked functional disturbance of the cochlear branch of the 8th nerve. About one-third of the cases with a vestibular disturbance are not accompanied by either shortened bone conduction or "subnormal" hearing.

*Involvement of the 8th Nerve and Type of Syphilis.* Alexander<sup>1</sup> states that the 8th nerve is involved in 20 per cent of those with latent syphilis and in 69 per cent of those with tabes and paresis, the latter figure being based on Krassnig's work. The distribution of the several forms of syphilis in our material among the 3 hearing groups is shown in Table 3.

TABLE 3.—HEARING GROUPS AND TYPE OF SYPHILIS.

Type of syphilis.	Hearing.			Total.
	"Normal."	"Excessive high tone loss."	"Subnormal."	
Early . . . . .	3	5	..	8
Late (excepting neurosyphilis) .	102	30	21	153
Neurosyphilis . . . . .	37	34	33	104
Congenital . . . . .	8	3	10	21
Total . . . . .	150	72	64	286

From it the incidence of nerve deafness in late syphilis (exclusive of neurosyphilis) would appear to be even greater than given by Alexander, and in neurosyphilis, including tabes and paresis, about the same as Krassnig gave. But since, as has been stated already, our material can in no sense be regarded as unselected, these values should not be considered as either confirmatory or contradictory.

Analyses of our cases from the standpoints of bone conduction and of vestibular reactions, as related to the several forms of syphilis, give results so similar to those for the audiometric data that these tabulations are omitted.

Reliable results were obtained in the same individuals for the bone conduction time and the vestibular reactions in 102 cases. In 18 of these are present all 3 of the most definite signs of involvement of the 8th nerve, *viz.*, loss of acuity for all tones by air conduction ("subnormal" hearing group), shortened bone conduction and impairment of vestibular reactions. The diagnoses for these 18 cases are: neurosyphilis, 12; congenital syphilis, 5; latent syphilis, 1.

*Spinal Fluid Studies.* Many observers have considered disturbance of function of the 8th nerve as evidence of central nervous system involvement in patients who had syphilis or in whom that diagnosis was suspected. Our material does not support this interpretation. The cerebrospinal fluid was examined in 106 of our patients with either "excessive high tone loss" or "subnormal" hearing. Thirty of these had late syphilis, exclusive of neurosyphilis, and the fluid was normal in all. In 64 with neurosyphilis the fluid was normal in 16 and abnormal in 48. Normal fluids were found in 11 of the 12 with congenital syphilis. Smith's<sup>5</sup> data are of interest in this connection; in a group of 33 congenital syphilitics with 8th nerve impairment, but without physical signs of neurosyphilis, the spinal fluid was abnormal in only 2. Obviously a diagnosis of neurosyphilis based only on impaired function of the 8th nerve in a patient with syphilis is not justified.

*Involvement of Other Cranial Nerves.* The function of other cranial nerves was impaired in 33 of our patients. The optic nerve was involved in 18; these patients are about equally distributed among our 3 hearing groups. In contrast to this, of 13 patients with facial nerve involvement, 8 are in the "subnormal," 3 in the "excessive high tone loss" and only 2 in the "normal" hearing group. The vestibular reactions were examined in 9 patients with facial paralysis and impairment was noted in 6, while this was true for only 2 of the 8 who were tested, who had optic nerve involvement.

*The Effect of Antisyphilitic Treatment.* Otologists and syphilologists are particularly interested in knowing what effect antisyphilitic treatment may have upon the hearing. Statistical reports by Beek<sup>2</sup> and Lund<sup>6</sup> and experimental studies by Ferretti<sup>7</sup> and others concerning the effect of arsphenamin and its various compounds point to the conclusion that the reported deleterious effects of these drugs have been exaggerated. Those patients with transitory

impairment of hearing following an injection probably suffer from a form of the Jarisch-Herxheimer reaction. Nerve deafness coming on 1 to 2 months following the inadequate treatment of early syphilis is considered to be not a toxic neuritis but a neurorecurrence. As to the beneficial effects of treatment, Alexander states that in 120 patients with congenital and acquired syphilis with impaired hearing, treated with neoarsphenamin and mercury, 8 per cent regained normal hearing, 42 per cent improved, 48 per cent remained unchanged and in 2 per cent the hearing became worse. Benario (quoted by Alexander) reported that in his cases of neurorecurrence the hearing was restored in 83 per cent while under treatment and improved in another 8 per cent; he regards the age of the patient and the method of treatment as important factors. Moore<sup>8</sup> noted improvement in all but 7 of 31 patients with neurorecurrence. Krassnig observed no improvement of hearing in deaf or partially deaf tabetics and paretics.

We have utilized two methods of approach in attempting to ascertain the effect of treatment upon hearing: (1) All of our cases have been grouped according to the amount of treatment received prior to the first audiometric examination and according to the hearing acuity at that time. (2) Those patients having 2 or more audiometric examinations have been analyzed separately from the standpoint of changes in hearing and the treatment received in the interval.

TABLE 4.—HEARING GROUPS AND AMOUNT OF TREATMENT.

Treatment.	Hearing.			Total.
	"Normal."	"Excessive high tone loss."	"Subnormal."	
Inadequate . . . .	118	55	55	228
Adequate . . . .	32	17	9	58
Total . . . .	150	72	64	286

The data obtained by the first method are presented in Table 4. The continuous plan of treatment outlined by Moore and Keidel<sup>9</sup> has been used. This consists of alternating series of an arsenical compound, usually arsphenamin, and a heavy metal, as a rule bismuth. The tabulation reveals that the majority of the patients had received little or no treatment before the date of otologic study. This is common to the 3 hearing groups. Only a small number are known to have had any treatment at all within 2 years following infection. Very few had received adequate\* treatment before the hearing examination; these are proportionately distributed among the three groups. Many observers believe that lesions of the 8th nerve have been due to treatment with arsenical compounds. Our material shows that the majority of those with "subnormal" hearing have had little or no previous treatment. In particular, we have

\* In this paper the treatment has been termed "adequate" on the basis of Moore and Keidel's definition.

no evidence in this series that in patients with already existing hearing difficulties the institution of treatment has been followed by further sudden abrupt deafness (Herxheimer reaction). Contrary to the widespread impression that inadequate treatment is more liable to enhance injury to the 8th nerve by syphilis, attention is called to the large number of such individuals in the "normal" hearing group.

On the whole, the above data justify the conclusion that in this group of patients no relationship is apparent between treatment and the development of hearing defects. Similar analyses from the standpoints of bone conduction and of vestibular reactions warrant the same conclusion.

Those patients having 2 or more otologic examinations are 61 in number. The intervals between the first and last tests vary from 2 months to 5 years, with an average interval of 2 years. There was no change in hearing in 52 of these, a diminution in 5, a slight improvement in 2 and marked improvement in 2.

The distribution as to hearing groups of the 52 whose hearing remained stationary is as follows: "normal" hearing, 23; "excessive high tone loss," 14; "subnormal" hearing, 15. Among these are 24 patients with late syphilis (excepting neurosyphilis), 24 with neurosyphilis, 3 with congenital syphilis and 1 with early syphilis. The amount of treatment was on the average the same for those in each of the 3 hearing groups.

Of the 5 patients whose hearing acuity decreased between the examinations, the loss in 3 is of the type that is characteristic of advancing age, being confined to the high tones; 2 of these had latent syphilis and 1 paresis. One of those with latent syphilis had received inadequate treatment; the other 2 had received regular treatment for about a year. The hearing acuity of 2 patients decreased for all tones; 1 had latent syphilis and 1 had involvement of the central nervous system. Both received adequate treatment. In both cases the vestibular reactions had also become impaired in the interval. The audiograms of the individual with the most striking change in hearing are given in Fig. 2. The patient is a colored man, aged 42, who gave no history of infection. The right facial nerve was paralyzed in 1925, and at that time he complained also of some impairment of hearing on the same side. The diagnosis made was central nervous system syphilis, unclassified. His hearing was first tested on March 3, 1930, after he had received adequate treatment, consisting as usual of alternating series of arsphenamin and bismuth. At that time bone conduction was not shortened and the vestibular reactions were "normal." Treatment was given regularly from that time until March 20, 1933. The audiograms of the ear that changed (Fig. 2) show the amount of loss for air conduction; the bone conduction had also become shortened and the vestibular reactions sluggish.

The slight improvement in hearing found in 2 cases was confined to the high tones; 1 had latent syphilis and received little treatment in the 6 months between the 2 otologic examinations, the other had tabes and received treatment continuously for over a year.

The audiograms of the 2 cases with improvement of a more marked degree are shown in Figs. 3 and 4. The greatest improvement observed was in a white woman, aged 29, who, while hospitalized

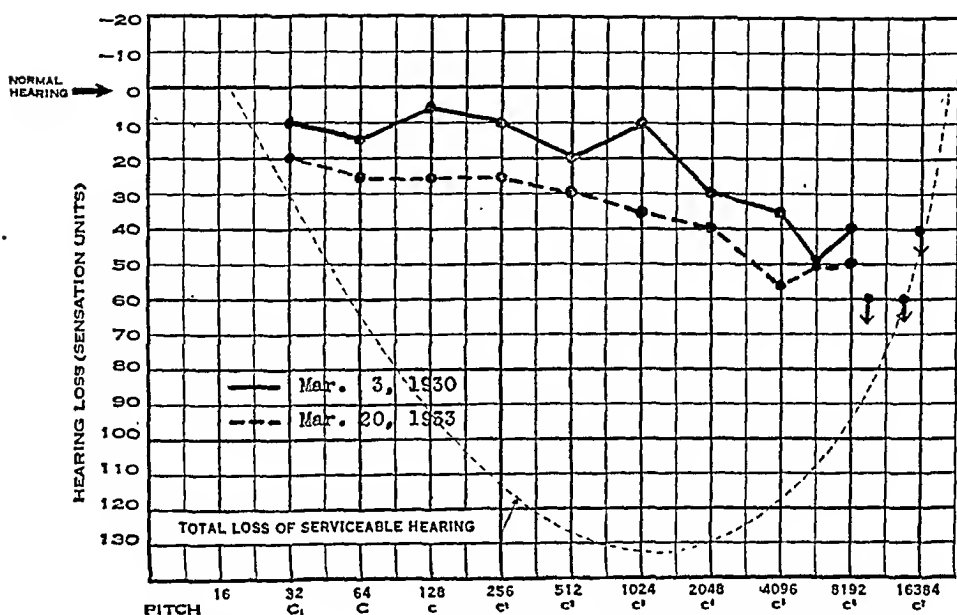


FIG. 2.—Decrease in hearing observed in a patient with neurosyphilis, unclassified.

for a fractured humerus, complained of a sudden disturbance in hearing. The audiogram of this date (December, 19, 1928, Fig. 3) shows a severe loss for air conduction; bone conduction time was also shortened. A vestibular examination was not made. She gave a questionable history of infection 2 months previously, for which she had received elsewhere 1 or 2 injections, probably arsphenamin. The blood Wassermann was positive and the spinal fluid negative. The recorded diagnosis was neurorecurrence. She was given weekly injections of arsphenamin (0.3 gm. each) for 6 weeks and then failed to return. The audiogram of March 9, 1933, 50 months after the first one, shows the marked improvement for air conduction; bone conduction was not shortened; the vestibular reactions at this time were normal.

Marked improvement, involving mostly the high tone region, was observed in a colored man, aged 26, who applied for treatment on September 9, 1931, with a genital chancre. During the next 5 months he received 4 injections of arsphenamin, the last one in February, 1932. Four months later he returned with a neuro-

recurrence involving the 5th, 7th and 8th cranial nerves. Both blood and spinal fluid Wassermann reactions were positive. At this time, June 7, 1932, the first otologic examination was made. The audiogram (Fig. 4) revealed a moderate degree of high tone loss; bone conduction time was not shortened; the vestibular

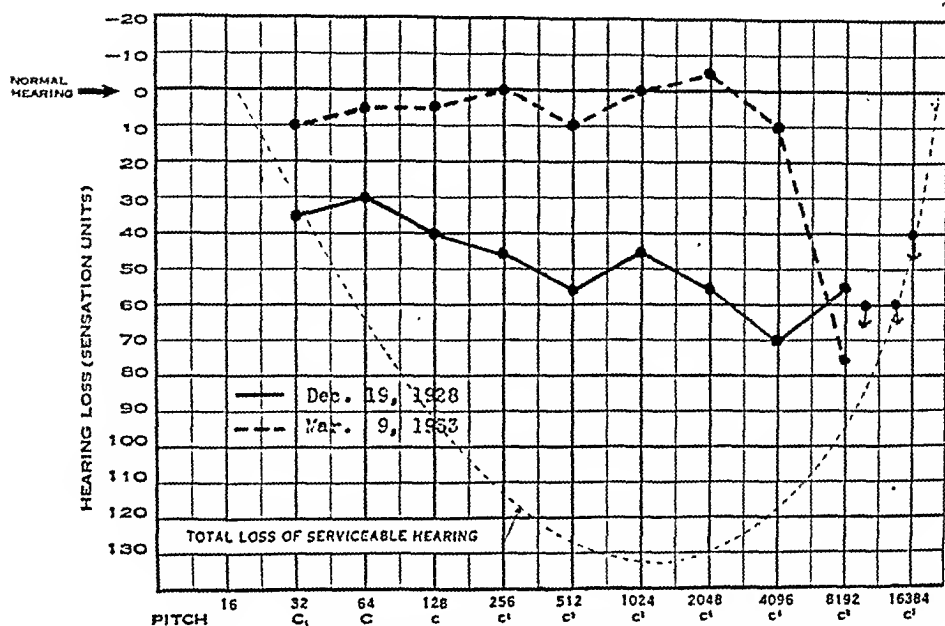


FIG. 3.—Improvement in hearing observed in a patient with early meningitis neurosyphilis (neurorecurrence).

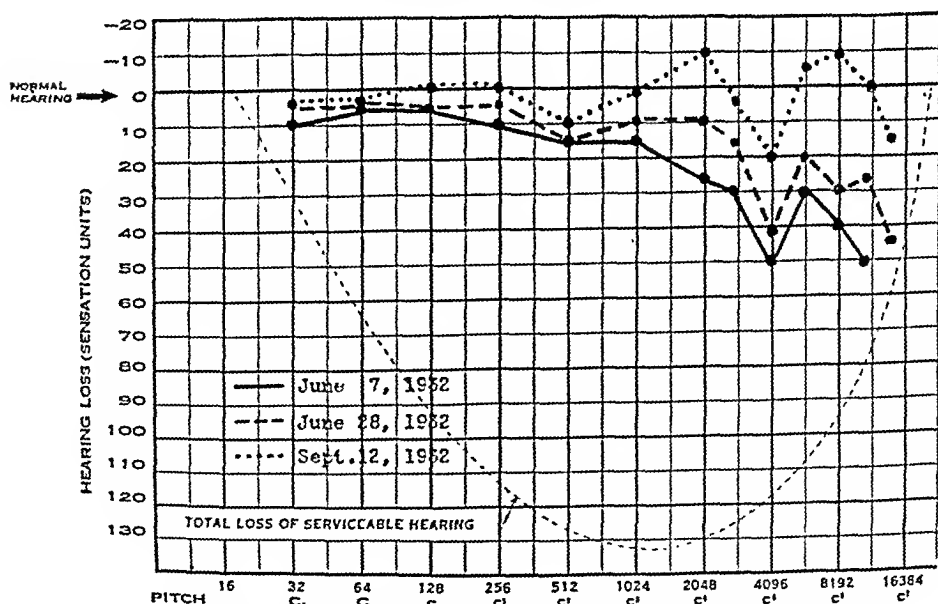


FIG. 4.—Improvement in hearing observed in a patient with early meningitis neurosyphilis (neurorecurrence).

responses were sluggish. Regular treatment was resumed. The audiogram made 3 weeks later (June 28) shows some improvement, and that of 3 months later (September 12) a return to good hearing. Vestibular reactions were now normal. During this 3 months he had received 14 injections of arsphenamin and 11 of bismuth.

Since the hearing remained stationary in 85 per cent of the 61 patients who had 2 or more otologic examinations, the number of those whose hearing changed is too small to warrant definite conclusions. However, 3 points are worthy of special note: (1) The number in whom impairment or improvement occurred is almost evenly balanced. (2) Even intensive treatment did not prevent a marked decrease in hearing in 2 patients with late syphilis. (3) The 2 cases with marked improvement had early meningeal neurosyphilis (neurorecurrence). That improvement in hearing may result from antisypilitic treatment in this type of neurosyphilis has long been recognized (Benario, Moore). In our material there are 9 cases of neurorecurrence with "subnormal" hearing; the 2 cited above showed improvement, in 2 others the hearing remained stationary under adequate treatment, the other 5 did not return for a second audiometric examination. Thus our findings with respect to neurorecurrence may be regarded as confirmatory of the clinical impression.

The few data preclude conclusions as regards the effect of treatment on impaired vestibular reactions. Thirteen cases with "impaired" vestibular function and 7 with "normal" function showed no change throughout the period of observation. Two previously "impaired," improved; 2 with "normal" reactions to begin with, showed impairment later.

Memmesheimer and Theissing,<sup>10</sup> and especially Krassnig,<sup>11</sup> have reported favorable results following the use of malaria in patients with involvement of the 8th nerve, the improvement becoming evident a few months after the treatment. Many of their patients had congenital syphilis. Eleven of our 61 patients who had 2 or more hearing examinations received malaria inoculations in addition to intensive treatment with arsphenamin and bismuth. The hearing examinations made on the average of 24 months later showed no change in any case.

This report constitutes, so far as we know, the first in which an audiometer has been used in an effort to study the effect of treatment on hearing in syphilis. As in all studies of hearing, we are impressed by the discrepancies between the subjective impressions of the patients and the actual measurements of hearing acuity. Some individuals complain of deafness when none can be demonstrated. Others already deaf report improvement in hearing which when tested for is lacking. We believe, therefore, that the frequency with which favorable effects are obtained by treatment, as reported by earlier workers, is open to question. Further audiometric studies are needed.



With the exception of early meningeal neurosyphilis (including neurorecurrence), both of the methods of analysis which we have used in studying our material as to the effect of antisyphilitic treatment upon the hearing lead us to the conclusion that it has no effect either beneficial or detrimental.

**Summary.** 1. A statistical analysis has been made of the otologic findings in 286 patients with syphilis, special attention being given to the effects of antisyphilitic treatment on hearing. All cases have been excluded in which there was evidence of middle ear infection or in which it was clear that the hearing defect antedated the acquisition of syphilis. Hearing by air conduction was examined with a Western Electric Company 1-A audiometer.

2. Shortened bone conduction in the presence of good hearing has not been observed except in cases of high tone loss.

3. Vestibular reactions have been found diminished in about 50 per cent of the cases with marked impairment of hearing. In this material about 33 per cent of the cases with diminished vestibular reactions are not accompanied by impairment of hearing.

4. Involvement of the 8th nerve is apparently more often associated with neurosyphilis than with other forms of syphilis.

5. Evidence is given to show that a diagnosis of neurosyphilis based only on impaired function of the 8th nerve in a patient with syphilis is not justified.

6. Comparison of the amounts of antisyphilitic treatment received by the patients here observed warrants the conclusion that there is no relationship between treatment and the development of hearing defects.

7. Sixty-one patients were reexamined otologically after an average period of 2 years; the hearing remained stationary in 52, improved in 4 and became worse in 5. The 2 showing most improvement both had early meningeal neurosyphilis (neurorecurrence); the 2 with greatest decrease had late syphilis.

8. With the exception of deafness associated with early meningeal neurosyphilis, it is concluded that antisyphilitic treatment has no effect on hearing, either beneficial or detrimental.

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## CONJUGAL SYPHILIS—A STATISTICAL STUDY.

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IN the natural course of events if one member of a married couple acquires syphilis the partner will become infected. In most instances this happens, but a certain proportion, larger than one ordinarily realizes, in some way escapes. Scant statistical data on conjugal syphilis is to be found in the literature. In fact, considering the large bulk of material bearing on syphilis, very little has appeared in this connection beyond interesting case reports.

Jordan,<sup>1</sup> reviewing 117 cases (husbands and wives), found that in 23 per cent syphilis was limited to the one first infected. He also felt that similar luetic manifestations in both were rare. It is stated by him that the one first infected is more inclined to neurosyphilis and that the one secondarily infected usually developed latent syphilis. Another finding was that if the one first infected did not have neurosyphilis the one secondarily infected was more liable to develop marked somatic syphilis. His opinion was that the treponema was attenuated during the development of neurosyphilis in the host. In his series he studied 100 cases (husbands and wives) in families where both partners were affected and found that 94 women were infected by their husbands and 6 husbands by their wives. Of the women, 72 developed active syphilis and 22 latent syphilis. The 6 men showed primary syphilis.

Kertesz<sup>2</sup> reported that in his series 50 per cent of the husbands of latent syphilitic wives showed treponema or treponematal elements in their spermatie fluid. Kertesz and Goldner<sup>3</sup> by intra-ocular injection of semen were able to produce syphilis in rabbits. The inoculum was obtained from patients with a history of syphilis and a negative serology or considerable treatment.

Dennie<sup>4</sup> felt that the age of the disease was the most important factor in its transmission. The older the infection the less danger of transmission existed. Physical examination showed evidence of the disease more frequently in the father than the mother. If marriage occurred during the first 5 years of the disease the woman ran a risk of infection. If the syphilis was of long standing in the father, the mother and children escaped.

Fournier<sup>5</sup> laid down certain conditions which should be fulfilled before permission to marry is granted. After some 50 years these rules are still applicable. Besides active treatment and clinical quiescence he emphasized the time element. Sir Jonathan Hutchinson<sup>6</sup> wrote, "Most authorities are agreed that, as a rule, patients who have reached the 6th year of their disease, although they may themselves be still liable to symptoms, do not transmit."

Galliot<sup>7</sup> was of the opinion that conjugal syphilis in the female was enough of a clinical entity to warrant a separate description. He found most frequently a form of latent syphilis with no symptoms other than positive serology or fetal accidents. To this he applied the term "forme fruste." Bertin<sup>8</sup> emphasized that this form of latent, often ignored, syphilis was of great importance because of the misfortune of hereditary syphilis. He also felt that prophylactic treatment should be given the contacts of these cases.

Payenneville<sup>9</sup> recommended that a husband or wife exposed to a syphilitic spouse be given a course of preventive treatment. He reported successful prophylaxis in 4 primary and 6 secondary cases and failure in 1 secondary case. Malherbe<sup>10</sup> reported a case in which the disease was transmitted from husband to wife during the initial incubation period. Levitin<sup>11</sup> mentioned a case of latent syphilis in a wife, the husband being free from infection. During the treatment of the wife the husband developed a penile chancre.

Pignet<sup>12</sup> recorded an instance of conjugal syphilis of the central nervous system with absence of mucocutaneous lesions in both husband and wife. He concluded that this bore out the neurotropic theory of Levaditi and Marie. Sezary,<sup>13</sup> however, felt that in conjugal neurosyphilis the law of coincidence, rather than a neurotropic organism, explains the nerve involvement. This form of syphilis is common and is bound to occur in both parties in a certain proportion of syphilitic marriages.

Hufschmitt<sup>14</sup> and Kloepfel<sup>15</sup> reported cases of conjugal syphilis in which the patients did not improve following the use of arsenicals, indicating to them an arsenic resistant strain of treponemata. Belgodere<sup>16</sup> cited 2 cases to show the vagaries of infection. One, a man, was exposed daily for 3 months to early syphilis in his mistress and failed to acquire the disease. The other, a woman, was infected by one illicit exposure.

Again quoting Sir Jonathan Hutchinson:<sup>17</sup> "There can be no duty more imperative, in the exercise of our profession, than that of abstaining from needlessly exciting in the minds of our patients suspicions as to conjugal purity."

When a married patient is admitted to our clinic, advice is given to bring in the spouse for a Wassermann test. This is not insisted upon too strongly nor is the other member questioned or instructed when appearing for the test. If the latter is positive the patient is registered for examination and treatment. If it is negative efforts are made to repeat the procedure at least twice. Incidentally the average dispensary patient is not anxious to bring in the spouse. Many of the negro patients registered as married are actually separated.

**Study.** In the syphilis treatment clinic of which I have charge in this hospital, an examination was made of 7896 records. Of this number, 4770 comprised married patients. Of these, both members

of the family were examined in 752 instances (376 husbands and wives). The husband alone was found to be infected in 60, the wife alone in 98, and both in 218 families. The interval between admissions of the two members of a family was interesting. It ranged from a few days to 8 years. In the instances of the longer intervals the spouse was admitted for some other condition and referred to the clinic because of a positive Wassermann test.

In considering the instances where both were infected the fact must be kept in mind that infection might have been acquired from sources other than conjugal. Many of these patients had latent syphilis, this was most common in the elderly negro. The initial lesion was disregarded, frequently called a "hair-cut," the secondary symptoms escaped notice, and the diagnosis was not made until the patient was admitted for some other reason and a routine Wassermann test made.

In only two instances did both husband and wife have neurosyphilis. It was felt that if a neurotropic strain of treponema existed a higher incidence of conjugal neurosyphilis would be present in this group. However, it must be remembered that most of these patients were negroes who develop somatic rather than neurosyphilis. In considering the type of syphilis as outlined in Table 4, one is led to the conclusion that individual resistance, rather than a strain of treponema, is probably the deciding factor.

In 41 per cent of this series one member escaped infection. It is felt that this is of importance because of the fear that has been generally disseminated concerning the infectivity of syphilis. The disease cannot be so extremely contagious, in the late stages, when a number approaching half of the husbands or wives in this group escaped. Also it would seem that the wife was less liable to transmit the infection since 38 more wives were syphilitic.

TABLE 1.—ANALYSIS OF MATERIAL.

Total records . . . . .	7,896
Married . . . . .	4,770
Single . . . . .	3,126
Husband and wife examined . . . . .	752
Both positive . . . . .	436
Husband positive, wife negative . . . . .	120
Husband negative, wife positive . . . . .	196

TABLE 2.—THE TYPE OF SYPHILIS CONCERNED.

	Husband positive, wife negative.	Husband negative, wife positive.	Husband positive.	Wife positive.
Primary . . . . .	7	1	22	2
Secondary . . . . .	7	8	32	38
Latent . . . . .	21	52	69	111
Tertiary . . . . .	20	23	52	37
Congenital . . . . .	1	9	0	4
Treated . . . . .	4	5	20	9
Undetermined . . . . .	0	0	23	17

In closing, a word of explanation concerning the tables. Table 1 shows the total records examined. Table 2 notes the types of syphilis in the entire series. Table 3 marks the interval between admission of patients. Table 4 shows the type of syphilis in the group with both infected. The term latent syphilis refers to those patients whose only symptom is a positive Wassermann test. The unclassified group are those who failed to register for examination.

TABLE 3.—THE INTERVAL BETWEEN ADMISSION FOR TREATMENT OF HUSBANDS AND WIVES.

	Husband positive, wife negative.	Husband negative, wife positive.	Husband positive, wife positive.
One week . . . . .	25	57	55
One month . . . . .	12	19	61
Three months . . . . .	12	12	44
Six months . . . . .	5	2	20
One year . . . . .	2	4	7
Over one year . . . . .	4	4	31

TABLE 4.—TYPE OF SYPHILITIC CONDITION WHEN BOTH HUSBANDS AND WIVES WERE INFECTED.

		HUSBANDS											
		Syphilis primary	Syphilis secondary	Syphilis tertiary					Latent	Congenital	Treated	Undetermined	
				Cardio-vascular	Muco-cutaneous	Central nervous system	Osseous	Visceral					
WIVES	Syphilis primary	1	1	0	0	0	0	0	0	0	0	0	
	Syphilis secondary	7	13	1	1	0	0	0	5	0	5	6	
	Syphilis tertiary	Cardiovascular	0	0	2	2	0	0	1	1	0	1	0
		Mucocutaneous	2	0	0	1	0	0	0	5	0	0	1
		Central nervous system	0	0	2	0	2	1	1	2	0	1	2
		Osseous	0	1	0	0	0	0	0	2	0	1	2
		Visceral	0	1	0	0	0	0	0	2	0	0	1
	Latent	9	12	4	7	8	2	8	42	0	9	10	
	Congenital	0	0	1	0	0	0	0	3	0	0	0	
	Treated	1	1	1	0	0	0	0	2	0	3	1	
Undetermined	2	3	3	1	0	2	1	5	0	0	0		

**Summary.** 1. There is presented an investigation of the records of 376 families in which syphilis was present in at least one member of the conjugal union.

2. Sixty husbands and 98 wives were syphilitic with non-syphilitic spouses.

3. In 218 families both husband and wife were syphilitic.

4. It is concluded that the type of syphilis depends upon the individual rather than upon any special strain of treponema.

5. Late syphilis is relatively non-infectious. Infectivity varies inversely with the duration of the disease.

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### THE PROBABLE ALLERGIC NATURE OF CINCHOPHEN POISONING.

WITH SPECIAL REFERENCE TO THE ARTHUS PHENOMENON AND  
WITH PRECAUTIONS TO BE FOLLOWED IN CINCHOPHEN  
ADMINISTRATION.

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THE toxic nature of cinchophen is now fully recognized, but the fact that this drug was studied in numerous laboratories and extensively used clinically here and in Europe for nearly 15 years before the first case of serious poisoning involving the liver was reported (Worster-Drought<sup>1</sup>) emphasizes the need for a more thorough understanding concerning the mechanisms of drug action. The similarity between cinchophen poisoning and allergic reactions has been noted by various writers.<sup>2, 3, 4</sup> Recently Short and Bauer<sup>5</sup> summarized 41 cases showing allergic reactions from cinchophen

and its derivatives, and added 4 more. The prominent findings repeatedly noted are: the polymorphous character of the skin eruption, the occurrence of edema, the frequency of fever, and the occasional profound vasomotor disturbance.<sup>3, 6</sup> Exacerbation of joint pains<sup>7</sup> and gastro-intestinal disturbances<sup>8</sup> have also been reported. Leukopenia, lymphadenopathy, and eosinophilia have not been conspicuous findings. Significantly, the hypersensitivity to cinchophen appears to be acquired, and even in those cases in which a reaction occurs following the first dose, exposure to cinchophen previously in the form of proprietary antirheumatic mixtures is quite probable, as Short and Bauer have pointed out. The sensitivity to cinchophen appears to be specific; and as Davis<sup>9</sup> has shown, a patient sensitive to cinchophen may show no reaction to neocinchophen, although he is more apt to acquire such a sensitivity than a normal individual.

**The Arthus Phenomenon.** Probably the most serious and most dreaded reaction resulting from the injection of a foreign protein is the so-called Arthus phenomenon,<sup>9</sup> a severe localized sterile inflammatory process resulting in necrosis at the site of a subcutaneous injection of a protein to which the animal has been previously sensitized. Further studies have shown that this definition is too narrow in that the process may occur in other than subcutaneous tissue; it has been produced experimentally in the lungs,<sup>10</sup> kidney,<sup>11</sup> joints,<sup>12</sup> heart and pericardium,<sup>13</sup> brain,<sup>14</sup> submucosa of the stomach,<sup>15</sup> and liver.<sup>16</sup> The possibility of producing a sudden anaphylactic inflammation with possible necrosis in an organ like the liver is of utmost importance. Since cinchophen can produce all the other known allergic reactions, it is logical to accept the possibility that the acute yellow atrophy or necrosis which it produces may be a manifestation of the Arthus phenomenon, especially since many of the cases showed a previous allergic hypersensitivity. Particularly significant is the fact that severe hepatic damage has resulted from relatively small doses,<sup>1</sup> whereas large doses over long periods in non-sensitive patients apparently produce little if any liver pathology. There is furthermore suggestive evidence that cinchophen may affect other organs. Petty<sup>17</sup> reported a case in which a patient after taking 10 pastilles of cinchophen developed an acute pancreatitis with fat necrosis and hemorrhage. The absence of calculi in the pancreas and the normal appearance of the biliary system makes it appear highly probable that it was a spontaneous process. It is also interesting to find that Feer<sup>18</sup> reported the occurrence of agranulocytosis following the use of nirvanol, a drug known for its frequent allergic side reactions. These considerations do not imply that every case of acute yellow atrophy is the result of an allergic reaction, but they do emphasize the possibility that the visceral damages resulting from cinchophen and perhaps many other drugs may be the result of an allergic inflammatory process which apparently is akin to the Arthus phenomenon.

The difficulty of accepting the anaphylactic nature of drug reactions has been due in great measure to the fact that substances like cinchophen do not give in sensitized individuals skin tests, precipitin reactions, and the Prausnitz and Küstner reaction. This objection, however, is not valid, for these reactions are probably not due to cinchophen but to a metabolic derivative. The drug in the body immediately undergoes chemical changes, presumably oxidation to a hydroxy compound and conjugation with glucuronic acid, which is a carbohydrate derivative. The work of Heidelberger and Avery<sup>19</sup> and of Goebel and Avery<sup>20</sup> has emphasized the importance of carbohydrates as determinants in antigenic substances. It is probable that the real hapten may be a glucuronic acid-oxycinchophen. Attention must also be directed to the marked modifications in physiologic action resulting from alterations in the cinchophen molecule. The iodo-cinchophens and the salicylate compound, atophanyl, seem to be more dangerous than cinchophen, while neo-cinchophen appears to be less prone to cause side reactions. Only a proper coördination of chemical and immunologic research can solve the problem under discussion.

**Precautions to be Observed.** By tentatively accepting, however, the idea that side reactions are allergic, certain precautions and rules can be formulated:

1. Any drug which is thought to produce hypersensitivity should be given only if adequate and continual medical supervision is possible. The patient should be instructed to watch for untoward symptoms and be told to stop the drug at the first sign of hives, loss of appetite, nausea, headache, dizziness, or malaise.

2. The practice of giving large doses followed by a rest period should be abandoned, for this practice seems to favor the development of hypersensitivity. No advantage accrues from the routine of Graham<sup>21</sup> which consists in giving the drug for 4 days followed by a rest period of 4 days. The use of sodium bicarbonate does not apparently minimize the danger of cinchophen (Evans,<sup>22</sup> Rabinowitz<sup>23</sup>).

3. Cinchophen and similar drugs should not be given to patients with a history of asthma or hay fever, or who are hypersensitive to foreign proteins. It is especially interesting that patients sensitive to salicylates may ultimately become hypersensitive to cinchophen as is illustrated by the cases of Davis<sup>8</sup> and Rabinowitz.<sup>23</sup>

4. The simultaneous administration of cinchophen and of a foreign protein such as vaccines or milk parenterally should be avoided. The danger of this is demonstrated by Rabinowitz's<sup>23</sup> series of cases. Davis emphasizes the danger of giving iodids with cinchophen.

5. There is no justification for the intravenous injection of cinchophen or of its derivatives. Recently the writer has obtained evidence that the intravenous administration of even small amounts of sodium salicylate can produce a sensitivity that could not be effected by large doses orally.



6. Drugs producing side reactions should be given with caution to patients with damaged livers. One must confess that the idea stressed by most writer that previous liver damage sensitizes the liver to cinchophen is not borne out in the reported cases. Weis<sup>24</sup> emphasized that the 3 fatal cases which he studied had no history of liver or gall bladder disease, and others have made similar observations. Nevertheless, there is the theoretical danger, for the liver is concerned with detoxication mechanisms and probably with the synthesis of immunologic substances. Cinchophen and allied drugs should not be given if a depletion of liver glycogen is suspected; but it must be remembered that there is no convincing proof that a liver abundantly supplied with glycogen is resistant to injury from cinchophen.

**The Treatment of Acute Yellow Atrophy.** Since this condition is really a massive necrosis, as Beaver and Robertson<sup>25</sup> have pointed out, treatment must be directed first to counteract the shock and toxemia resulting from the absorption of necrotic tissue, and second to take care of the hepatic insufficiency resulting from the extensive destruction of parenchymatous tissue. If the patient can be tided over the crucial period, the chances of recovery are good, due to the great regenerative power of the liver. If the patient cannot retain food, glucose should be given parenterally. Small doses of insulin, 5 to 10 units 3 times a day, have been recommended by various writers. It may be tried, although the results of this treatment, as shown by various case reports, have been disappointing. If the blood sugar falls below 80 mg. the administration of glucose intravenously is indicated. Calcium in the form of calcium gluconate should be given intravenously or intramuscularly, and by mouth. While the evidence for the clinical value of calcium in this condition is still fragmentary, the rationale for its use is based on its protective and restorative action on the liver in carbon tetrachlorid poisoning,<sup>26</sup> and on the fact that calcium modifies allergic reactions. The use of liver extract as recommended by Bassler<sup>27</sup> should be included in the treatment. The diet should be very low in fat and also low in proteins, because of the loss of the deamination power of the liver. Skimmed milk and other milk products low in fat should be given, if tolerated, since milk is especially rich in calcium. Gelatin in the form of desserts should be given several times a day, for this food is easily assimilated and contains a high percentage of the amino acid, glycine. This compound is normally synthesized by the liver and is important in the detoxication processes and probably has other important physiologic functions. The use of sodium lactate has been advocated by Weigeldt,<sup>28</sup> but in view of the fact that the accumulation of lactic acid in the body occurs in certain metabolic dysfunctions involving the liver, this form of therapy seems distinctly illogical. The kidney condition, characterized by a marked albuminuria and nitrogen retention,

which is frequently observed in severe cases, is probably secondary to the liver damage, a form of renal hepatic syndrome similar to the one studied by Helweg and Schutz.<sup>29</sup> As a general rule it requires no special treatment. A number of authors have considered the possibility of surgical drainage in acute yellow atrophy, but there is not enough available data to draw any definite conclusions. It should be mentioned, however, that the case of acute pancreatitis reported by Petty<sup>17</sup> had surgical drainage of the pancreas and, in spite of the seriousness of the condition, the patient recovered.

**Case Abstracts.** CASE 1.—With a marked acute allergic attack. (Patient of Dr. S. Thompson.) A white woman, aged 36, developed an arthritis of the joints of her first toe. Guphen, a proprietary cinchophen derivative (the guaiacol ester of cinchophen), was given (1 tablet t.i.d. for 10 days). After a rest period of 10 days, the patient, because of the return of pain, took 1 tablet of guphen. About 30 minutes later she developed a sudden attack of palpitation, dyspnea, numbness and tingling of her extremities. There was edema about her eyes and the skin had a scarlet hue. Adrenalin eased her symptoms, and recovery occurred promptly. Skin tests of all articles of food eaten on that day as well as of guphen were negative.

The similarity of the clinical picture to foreign protein shock is evident. Sutton<sup>6</sup> and Barron<sup>3</sup> have described similar cases in which cinchophen was the cause of the profound vasomotor disturbance. The present case furnishes further evidence that no cinchophen derivative is entirely safe.

**Atypical Cases of Cinchophen Poisoning.** The present literature on cinchophen fails to emphasize that the drug may produce hepatitis without jaundice. If therefore it occurs concomitantly with another pathologic condition which may also produce liver damage, it may easily be overlooked. The following 2 cases will serve as possible illustrations.

CASE 2. (From the Surgical Service of Dr. F. W. Bancroft.)—Miss B., aged 60, has a history of asthma, hay fever, and symptoms of cholecystitis of many years' duration. Cholecystectomy and appendectomy, March 12, 1931. During the past year, she noticed brown pigmented areas over her intercostal angle and back. A few weeks before admission to the hospital, she developed dyspnea, nausea, cyanosis, and increasing weakness. On examination it was found that her heart was moderately enlarged, but gave no signs of valvular defects. Blood pressure: 158 systolic and 108 diastolic. The liver was markedly enlarged but not tender. The electrocardiogram showed a right axis deviation. Icteric index was 10.7. A test of liver function<sup>30</sup> was 46 per cent normal. Other laboratory findings were essentially normal. The condition was considered as cardiac failure with chronic passive congestion of the liver, until it was learned that the patient for the past year had begun taking neocinchophen instead of aspirin. Occasionally she took as many as 3 tablets daily, but the total amount was not large. Treatment consisted in giving calcium gluconate, and liver extract by mouth. A small amount of digitalis was also given. A high carbohydrate, low fat diet was prescribed. One month later her liver func-

tion as measured by the writer's test was 70 per cent of normal. Recently the patient's tolerance for fats has been definitely increased by feeding small amounts of bile salts. Clinical improvement has progressed very slowly.

CASE 3. (From the Medical Service of Dr. C. F. Tenney.)—Mrs D., aged 32, a Puerto Rican, 2 years ago had a positive Wassermann reaction, which after 2 courses of antiluetic treatment (neoursphenamin and bismuth) became negative. A miscarriage occurred 5 months ago. Two weeks before admission she developed a polyarthralgia, which was diagnosed as acute rheumatic fever, and cinchophen was prescribed (16 tablets in 6 days). She also received an intramuscular injection, but efforts to learn the nature of the agent injected were unsuccessful. Four days after stopping the medicine, she had a sharp pain in her left chest, pain and tenderness over her epigastrium, nausea and vomiting. At the time of her admission to the hospital, she was in a precomatose state. On examination, the sclera showed no icteric tinge, the heart was slightly enlarged to the left, the heart sounds lacked tonus, the second aortic was feeble, even though her blood pressure was 180/140. Scattered crackling râles were heard at the bases of her lungs, and a definite friction rub over the left anterior chest. The liver was greatly enlarged, extending below the umbilicus. It was soft and not tender. No ascites. Urine showed 4+ albumin, but no casts nor bile pigments. Blood chemistry: non-protein nitrogen 54 mg., uric acid 5.0 mg., creatinin 1.9 mg., sugar 125 mg. per 100 cc. of blood. Icteric index 7.5. Treatment consisted in daily hypodermoclysis of 5 per cent glucose until vomiting stopped, intramuscular injections of calcium phosphate and of liver extract. One transfusion and several short-wave treatments were also given. The diet consisted mainly of milk, gelatin, and orange juice. Marked clinical improvement began on the 8th day; the heart sounds became normal; the blood pressure dropped to 146/108; the nausea subsided; and the temperature became normal.

There are good reasons for accepting that neocinchophen and cinchophen respectively were the immediate causes of the liver condition in the above cases. If the insidious nature of cinchophen poisoning had not been known, it is highly probable that other diagnoses would have been made, the first case as passive congestion due to cardiac failure, and the second case perhaps as luetic cirrhosis or atypical pneumonia. One can venture to predict that the first patient, had she continued to take neocinchophen, would have succumbed to the hepatitis. It appears that recovery in cinchophen poisoning is greatly retarded if any contributory cause of liver damage like cardiac failure or lues is present. These conditions undoubtedly impede the regenerative power of the liver.

**Summary.** The probable allergic nature of cinchophen poisoning is discussed and the hypothesis is presented that the acute yellow atrophy caused by this drug may perhaps represent a special form of the Arthus phenomenon.

Precautions in the use of drugs known to produce side reactions are outlined and treatment of acute yellow atrophy is described.

A case of an acute allergic reaction (from guphen) and 2 cases of atypical cinchophen poisoning with hepatitis but no jaundice are presented.

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## NEVUS FLAMMEUS NUCHÆ; ITS OCCURRENCE AND ABNORMALITIES.

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ONE of the commonest congenital defects of the skin is the variety of flat angioma known as nevus flammeus nuchæ. Interest in this minor deviation from the normal was induced by encountering a number of superimposed skin conditions which had apparently developed at some later period than that when the nevus had originally been noted.

The appearance of the unaltered angioma varies in size, depth of color and type of configuration but seldom is there much change in the location. This usually adheres strictly to the region on either

side of the posterior midline and is fairly symmetrical in outline. In the majority of cases it is entirely included in a cephalo-caudal dimension between the occipital protuberance (inion) and the tip of the spine of the 5th cervical vertebra. The long axis of the appearance is usually up and down. Frequently one is somewhat confused in the classification of these cases by instances of mottling produced by vitiligo, old sunburn, scars, and the hypertrophic weather-beaten skin of the aged. Faint pinkish marks may mean a trivial degree of the condition. Pressure is frequently of distinct use in ruling out these somewhat suggestive appearances and none were included in the list as positive findings if there was any doubt as to their true nature. A geographical type of broken-up, jutting, indented and, in a small degree, marginal insular configuration is the rule. Seldom is the area of the nevus of a compact form; usually the edges are lacy. Frequently there is a marked similarity to the blot produced by gently pressing a folded paper with an ink-drop in the crease and then opening it flat again. Elevation is not found in this form under discussion; its presence automatically removes the case into another vascular category. The color varies from light pink to a purplish red. Often it corresponds fairly accurately to the natural color of the lips of the subject. The frequency of occurrence in the adult has been inquired into and would appear to be greater than its incidence in the newborn although my impression formerly had been somewhat the reverse. The well-known fact that many angiomas appear some time after birth may have its bearing in this connection.

In a group of medical students, out of 275 individuals examined, typical nuchal nevi were found in 13 instances (4.7 per cent). In a skin dispensary, 100 adult patients, 50 consecutive of each sex gave a count of 8 (4 in each sex). Of 175 casual examinations 10 had nevi (5.7 per cent). On the other hand, 210 babies, routinely examined the day after birth in a maternity nursery showed but 6 to have a nevus at the back of the neck (2.8 per cent) though there was numerous such appearances elsewhere, notably the eyelids. The percentage in the adult cases showing the mark was 5.6. Grouping these 760 cases without respect to age the incidence of this condition was found to be 4.8 per cent, a very considerable proportion of mankind and probably an underestimation of the actual figures if intermediate ages were included. Search of the literature of the past 15 years gives no reference to the condition.

The mark is, of course, most readily apparent in males and in severely bobbed females but the matter of sex does not appear to affect the incidence of the condition. The practice of wearing the hair long, however, does seem to alter the mark and indirectly induce changes in the abnormal skin of that region. The hair of the affected region appears to be uninfluenced by the mark and grows normally, hiding the defect unless it is kept in a close clipped condition. Of 8 individuals not included in the above figures, con-

sulting me for skin outbreaks overlying nuchal nevi, 7 were women. Of these, 5 had long hair worn in a knot at the back of the head at least some part of each day. All of the 5 were over 40 years of age. In all of the 8 cases cited there was at one time or another, during my observation of the case, a clear diagnosis of a nuchal nevus serving as a base for the more recent outbreak.

**Case Abstracts.** CASE 1.—C. W. F., a white man, aged 52 years, an insurance agent, consulted me March 23, 1931 on account of a small swelling which had occurred at the edge of an old birthmark, a port wine stain in the midline of the back of the head just above the posterior hair line. The mark was of a purplish color and the elevation somewhat of a darker shade

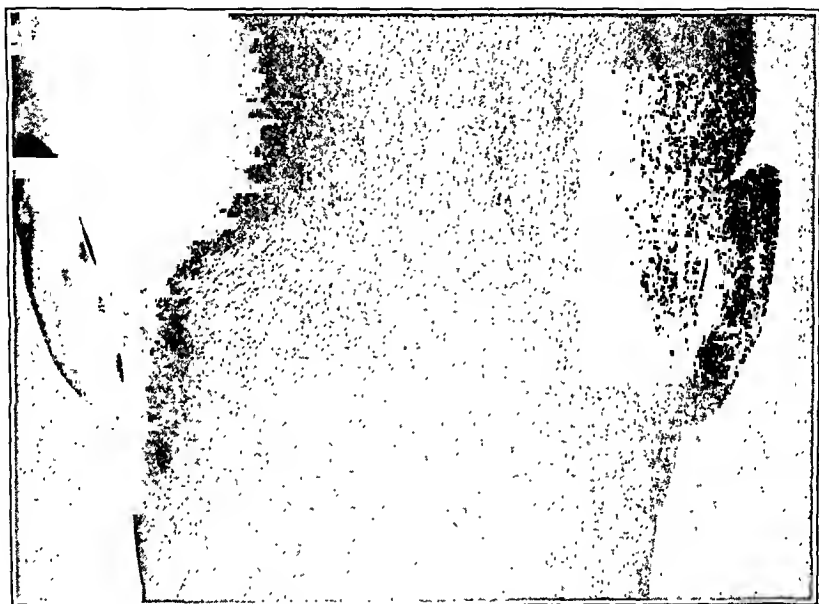


FIG. 1.—Typical nuchal nevus.

and the size of a grain of wheat. He had noticed its presence for several weeks. Permission for a biopsy was refused so, after preliminary radiation by Roentgen rays, which only caused slight flattening of the growth, it was destroyed by electrodesiccation under novocain anesthesia. The growth was solid and firm and after destruction left a smooth scar. In November of the same year a similar appearance was noted about an inch (2.5 cm.) from the old scar and also situated on the angiomatous base. It was treated in a similar fashion. In the course of the next year, 1932, two more areas distinct from either of the former sites became elevated and were treated with radium, causing them to flatten down and separate as scales leaving some underlying infiltration which was fulgurated. No more lesions of this type have been seen to date (June, 1933) though a few pustules were apparent on the normal skin around the nevus in September, 1932. These were follicular infections and discharged their contents.

CASES 2 and 3.—F. C., a white school girl aged 11 years, was brought to the office for a crusted eruption at the back of the neck within the hairy area. It had existed off and on for several years and was quite itchy. No pediculosis was present and but a moderate amount of seborrhea. Under treatment there was a rapid improvement and disappearance of the crust with the emergence of an underlying *naevus flammeus* heretofore masked by the dermatitis.

The mother, Mrs. W. D. C., aged 41 years, had an identical mark in that situation with some scaliness and itching. There were a few areas of seborrheic dermatitis in her scalp. She had been told from childhood that she had a strawberry mark at the back of her head. (Another daughter [sister to F. C.] had a large pigmented and hairy nevus on the outer side of her left lower leg). Hairpins were used in a knot covering the nevus and sometimes were employed to scratch the scaly area.

CASE 4.—Mrs. S. B. W., a white woman aged 65 years, had had "eczema" at the back of her head for years; 20 at least. Examination showed an irregular but margined patch in the hairy area in the midline, spreading symmetrically on both sides. It measured 2 inches up and down and 1½ inches across at its greatest extent. Some crusts were apparent on the surface and superficial excoriations. After 2 weeks' treatment the superficial inflammation had subsided and there was plainly apparent a typical nuchal nevus. A knot secured by composition (sometimes metallic) hairpins covered the very area affected. Roentgen ray, in dosage insufficient to cause epilation, was most beneficial in causing a subsidence of the eruption.

CASE 5.—F. L., an unmarried white woman, aged 53 years, had had an irritated area at the back of the scalp for several years. Her hair was kept short partly on this account as she found that long hair heated the patch and increased itching. The area resembled psoriasis somewhat, though there were no other evidences of that disease on any other part of the body. Roentgen ray and a tar lotion caused a disappearance of the scale and allowed one to identify a port wine mark in that region, previously masked by the exfoliation. Heretofore its redness had been thought to be due to the inflammatory base of the outbreak.

CASE 6.—Mrs. C. M. H., aged 52 years, white, had suffered from scalp irritation for a number of years. There was a distinct nuchal nevus with, in places, a scaly eczematoïd eruption overlying it. In addition a seborrheic dermatitis was present over the right ear. No appearance of psoriasis was to be noted on the body, and the scalp outbreak was in no wise indicative of that disease. The birthmark had been present from early childhood, she had been told. Her hair, while thin, was long and knotted in the back with metal hairpins.

CASE 7.—Mrs. A. K., aged 48 years, was practically identical with that preceding in all respects save that seborrheic dermatitis elsewhere was not present.

CASE 8.—Mrs. M. N., white, aged 62 years, came for relief from a sharply margined seborrheic dermatitis affecting the scalp, neck and postauricular areas. In the latter region there was oozing and crusting, elsewhere the outbreak was a sheet of dull red with a thin, cracked, brownish-yellow scale on the surface. The history was definite as to the presence of a "strawberry mark from childhood" with the added eruption appearing on its surface 2 years ago and spreading centrifugally to its present dimensions.

**Summary.** 1. From examination of 760 individuals it would appear that nuchal nevi occur in about 5 per cent of the population and are to be noted more frequently in the adult (5.6 per cent) than in the newborn (2.8 per cent).

2. While the impression exists that the two sexes are about equally affected by the nevus, it served as a starting point for inflammatory outbreaks mainly in long-haired individuals, the short-haired being for the most part unaware of its existence. Hairpins may have had some influence in the production of secondary irritation.

3. The usual outbreak on this abnormal skin is of the nature of a dermatitis, seborrheic or eczematoïd, with an occasional resemblance to psoriasis.

## REVIEWS.

**PATHOGENIC MICROÖRGANISMS.** By WILLIAM HALLOCK PARK, M.D., Professor of Bacteriology and Hygiene, University and Bellevue Hospital Medical College, and Director of the Bureau of Laboratories of the Department of Health, New York City; and ANNA WESSELS WILLIAMS, M.D., Assistant Director of the Bureau of Laboratories of the Department of Health, New York City. Pp. 867; 215 engravings and 11 full-page plates. Tenth edition, enlarged and thoroughly revised. Philadelphia: Lea & Febiger, 1933. Price, \$7.00.

"Our experiences to date with active immunization against diphtheria and scarlet fever are given. . . . The recent additions to our knowledge of yellow fever, poliomyelitis, bacteriophage, undulant fever, etc., have received due attention. . . . The comprehensive summary table has been continued and revised, since many have continued to express appreciation of it. This table gives the essential characters of and pathologic conditions caused by each of the commoner bacteria. . . . The bibliography has been added to." (From Authors' Preface.)

**THE BIOLOGY OF THE PROTOZOA.** By GARY N. CALKINS, PH.D.; Sc.D., Professor of Protozoölogy, Columbia University. Pp. 607; 223 illustrations, and 2 colored plates. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1933. Price, \$7.50.

THE author maintains much the same style of presentation as in the first edition. More important changes consist in omitting discussion of chlorophyll-forming flagellates, and the addition of a chapter on parasitic protozoa. The latter is incomplete and uncritical. There also has been extensive rearrangement of other subject matter, and revision of taxonomy. H. R.

**STARLING'S PRINCIPLES OF HUMAN PHYSIOLOGY.** Edited and revised by C. LOVATT EVANS, D.Sc., F.R.C.P., F.R.S., Jodrell Professor of Physiology, University College, London. The chapters on The Central Nervous System and Sense Organs revised by H. HARTRIDGE, M.A., M.D., Sc.D., F.R.S., Professor of Physiology at St. Bartholomew's Medical College. Sixth edition. Pp. 1122; 562 illustrations, 10 in color. Philadelphia: Lea & Febiger, 1933. Price, \$8.75.

THE extensive use of this book since its first appearance, in 1912, has proved its high merit as a textbook for medical students and for those who are specializing in physiology. Since Starling's death, the two revisions by the present editor, who occupies the chair previously held by Starling, have increased its usefulness as a textbook and book of reference in this rapidly changing field of science. This latest (6th) edition, appearing three years after the 5th, contains notable improvements, in textual revision, discussions of very recent experimental work, and addition of many new illustrations. A new feature is the notation of specific references, which makes it possible to locate more easily the sources of statements made; and, because of the discrimination in the selection of this bibliography, guides the reader to the more important contributions in current literature. I. Z.



**A GERMAN DOCTOR AT THE FRONT (DIE FRONT DER ARZTE).** By PROFESSOR DR. WILHELM HIS; translated from the original German by COL. GUSTAVUS M. BLECH, Medical Corps, Reserve, and BRIG. GEN. JEFFERSON R. KEAN, Medical Corps, U. S. A. (RETIRED). Pp. 230; 1 illustration. Washington, D. C.: The National Publishing Company, 1933 (American edition). Price, \$2.50.

ALTHOUGH the distinguished author of these reminiscences states that their purpose is rather to draw useful lessons from his war experiences than to entertain, they provide much of interest in both directions to anyone desirous of knowing how the other half lived while the fire curtain was down. The Swiss son of an eminent Swiss anatomist many years professor at Leipsic, the younger His became a naturalized German citizen in 1906, and was professor of internal medicine at the Charité, Berlin, when the war broke out. Volunteering early, he saw active service on both Eastern and Western Fronts, in Turkey, Mesopotamia, Persia, Palestine and the Ukraine. His cosmopolitanism adds color to the narrative and authority to such reasoned optimism as that the World War should be regarded, not as the greatest of human catastrophes, but as the greatest of human experiences. The tenacity displayed by all sides is sufficient evidence to him that the civilized world, far from degenerating, may have found in the experience of the war the kernel of their future happiness. To one who, like the author, has cut his investigative teeth on the bundle of His, if such a barbarism may be permitted, this work appeals with special emphasis. That it should be translated and promoted by two medical officers of the U. S. Army is but another demonstration that good fighters or even good hating fighters are not apt to continue the fight or hate after the quarrel is over.

E. K.

**HISTORY AND SOURCE BOOK OF ORTHOPÆDIC SURGERY.** By EDGAR M. BICK, M.A., M.D., Adjunct Orthopædic Surgeon, Hospital for Joint Diseases, New York City; Adjunct Orthopædic Surgeon, Montefiore Hospital, etc. Pp. 254; illustrated. New York: The Hospital for Joint Diseases, 1933. Price, \$1.50.

THE Hospital for Joint Diseases is to be commended for this demonstration of its breadth of purpose and congratulated in these times of enforced economies on its successful adaptation of the photographic format of book-making in lieu of the more expensive printing. We heartily agree also with Dr. Brackett's introductory remarks on the pleasure and profit of sometimes going back to the past, in order to examine the steps in our progress to our present position and to praise famous men. The author has followed the chronologic approach for the first 5 chapters; and in the next 6 considered the modern period from the points of view of physiology, pathology, methods of practice in bone, joint and muscle-tendon surgery, non-operative orthopedics, with a final chapter on the rise of orthopedic hospitals and institutions.

E. K.

**LYMPHATICS, LYMPH and TISSUE FLUID.** By CECIL K. DRINKER, B.S., M.D., Professor of Physiology, Harvard School of Public Health, and MADELEINE E. FIELD, A.B., PH.D., Instructor in Physiology, Harvard School of Public Health. Pp. 254; 11 illustrations and various tables. Baltimore: The Williams & Wilkins Company, 1933. Price, \$3.00.

THIS is an interesting and even entertaining monograph on the physiology of lymph and lymphatics. The authors bring good experimental knowledge and acquaintance with the literature which, combined with a real gift for writing, has produced a valuable review. The chief subjects covered are

the structure and permeability of lymphatics, the permeability of blood capillaries, the composition of lymph and the flow of lymph in health and disease. Many controversial points arise, for example, the effect of inflammation on the flow of lymph; on these points the authors, while presenting all points of view, state their own opinions freely. There is a well-arranged bibliography.

M. McC.

**HUMAN VALUES IN PSYCHOLOGICAL MEDICINE.** By C. P. BLACKER, M.C., M.A., M.D., M.R.C.P. Pp. 179. New York: Oxford University Press, 1933. Price, \$2.50.

THE purpose of this book is to elaborate in the field of medical psychology further material regarding concepts of values as related to the life, personal characteristics and idiosyncrasies of the psychiatric patient. Secondly, an attempt is made to relate the principles of psychologic medicine to those of biology. The book attempts to link philosophy to medical psychology, with special reference to psychoanalysis and occasionally to the practice of psychiatry. The concept of values as experienced by the individual is elaborated with emphasis on the idiosyncrasies individuals possess rather than their similarities to others.

Chapter IX, on the productive, the transmissive and the reactive conceptions of value, summarizes most of the material of the book and gives it its closest tie-up with clinical psychiatry. The last chapter, "Life and Death Instincts," bears little relation to the rest of the book. Here the author cleverly attempts to refute Freud's discussions on the death instinct, though his grounds will not be accepted by orthodox Freudians.

The book is of value to those who are interested in the theoretical aspects of psychiatry and psychologic medicine. It has no practical clinical value.

L. S.

**PARALYSIS IN CHILDREN.** By R. G. GORDON, M.D., D.Sc., F.R.C.P. (Ed.), Physician, Bath and Wessex Orthopaedic Hospital; Physician, Royal United Hospital, Bath, etc., and M. FORRESTER BROWN, M.D., M.S. (Lond.), Surgeon, Bath and Wessex Orthopaedic Hospital; Surgeon to County Orthopaedic Clinics, Wiltshire, Somerset, and Dorset. Pp. 328; 116 illustrations. New York: Oxford University Press, 1933. Price, \$4.50.

WHILE not broad in its scope, this work concerns itself with that borderland where neurology and orthopedics meet.

The subject-matter is considered under three headings: General, including the physiology of movements, the incidence of lesions, the causes of paralysis and the diagnostic significance of physical signs. Clinical, illustrating the various syndromes by cases and showing the difficulties in diagnosis and treatment. Treatment, giving in detail the physiotherapy and non-operative orthopedics.

The book is abundantly and aptly illustrated and will prove very helpful to those interested in paralytic children.

N. Y.

**A SYNOPSIS OF SURGERY.** By ERNEST W. HEY GROVES, M.S., M.D., B.Sc. (Lond.), F.R.C.S. (Eng.), Consulting Surgeon to the Bristol General Hospital; Emeritus Professor of Surgery, Bristol University. Pp. 693; 64 illustrations, 13 colored plates. Tenth edition. New York: William Wood & Company, 1933. Price, \$5.00.

THIS well-known work has been revised to include the newer knowledge of the surgery of the sympathetic nervous system and the Orr treatment

of compound fractures and osteomyelitis. A new chapter, wherein the principles of amputations are outlined, has been added, which presents this material in one section rather than scattered through the book as in previous editions. These subjects have been dealt with, as have all other topics in the book, in brief abstract form.

The conciseness of this work requires that its presentation. As an outline of Rose and Carless' it presents the salient facts presented there. One can no more obtain the same perspective from an outline as from the original than one can from a rough sketch as from a finished painting. To those studying surgery for the first time, this book, like "a little knowledge," is dangerous. To the individual who has a thorough knowledge of surgical literature, this book will be useful for refreshing the memory for facts forgotten. For the student who hopes to cut short hours of study, it will afford a skeleton of information, but here too it should be used only as should lecture notes. I. R.

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THE TECHNIQUE OF LOCAL ANESTHESIA. By ARTHUR E. HERTZLER, A.M., M.D., PH.D., LL.D., F.A.C.S., Professor of Surgery, University of Kansas; Surgeon to the Halstead Hospital, Halstead, Kansas, and to St. Luke's Hospital and St. Mary's Hospital, Kansas City, Mo., and to the Providence Hospital, Kansas City, Kansas. Pp. 292; 148 illustrations. Fifth edition. St. Louis: The C. V. Mosby Company, 1933. Price, \$5.00.

THE fifth edition of Hertzler's monograph follows the same outline that has been used in previous editions. After preliminary discussion of the drugs and their actions, he discusses the technique of anesthesia according to the anatomic position in the body. Neuroanatomy of each region is briefly reviewed, followed by a description of the technique of placing the anesthetic solution. A new section on spinal anesthesia has been written by Dr. A. E. Spelman, and a short chapter on intravenous anesthesia, using the barbiturates, has been added by Dr. Raymond F. Gard. The book contains many drawings and photographs illustrating the techniques discussed. There are several notable omissions, for instance, paravertebral anesthesia in angina pectoris. The book fills a place as a reference work for those who wish to learn the technique of local anesthesia.

L. F.

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THE OPERATIVE STORY OF CLEFT PALATE. By GEORGE MORRIS DORRANCE, M.D., F.A.C.S., Professor of Maxillofacial Surgery, The Thomas W. Evans Museum and Dental Institute School of Dentistry, University of Pennsylvania; Surgeon to St. Agnes' Hospital and to the American Oncologic Hospital, Philadelphia. Assisted by ENAYAT SHIRAZY, D.D.S. Pp. 564; 534 illustrations. Philadelphia: W. B. Saunders Company, 1933. Price, \$6.50.

FROM a historical point of view the author and his assistant have, by collecting the data which are presented in this volume, done a monumental piece of work. The book is what it is designated, "The Operative Story of Cleft Palate." From this standpoint it will make an excellent reference work.

Throughout the historical sections of the work, however, the reportorial style has been used, and no attempt has been made to collate the material in an easy biographic sequence. Quotation marks are used as on page 1, in discussing Celsus, with no reference as to the author quoted. Sentence construction is often stilted, and more than once grammatically incorrect. In the preface, "Dr. Joseph Sweet" should have been Dr. Joshua Sweet, and "Muetter Museum" on page 371 should have been Mütter Museum.

There are numerous evidences of this sort which suggest a laxity in proof-reading.

The illustrations must be discussed from two angles. Those collected from the literature for which the author has no responsibility except for their selection. Many of these are of great historical interest. The Reviewer does, however, believe that many of the collected illustrations may have been omitted. The illustrations which the author presents as original are of unusual excellence.

The final chapters of the book which deal with the Applied Anatomy and Pathology of Split Palate, The Occurrence and Distribution of Split Palate, the chapters on the Operative Treatment of Cleft Palate and the one on Conclusions are written in a much better style. In the operative field, the author has made valuable contributions, and he has given a clear description of his "push-back" operation. The chapter on The Rôle of Speech in Split Palate Patients covers a scant  $2\frac{1}{2}$  pages. The subject is too important to have been given so little space. The bibliography covers 87 pages and is the most complete yet published.

This book will prove a valuable reference book for surgeons and medical historians.

I. R.

**SURGERY OF THE STOMACH AND DUODENUM.** By J. SHELTON HORSLEY, M.D., F.A.C.S., LL.D., Attending Surgeon, St. Elizabeth's Hospital, Richmond, Va. Pp. 260; 136 illustrations. St. Louis: The C. V. Mosby Company, 1933. Price, \$7.50.

THIS delightfully written monograph was dedicated by the author "To my Colleague and Rival, Stuart McGuire, Gentleman, Master Surgeon." On the Reviewer always falls the task of expressing himself as to whether a given work is merely just another volume to review or whether the work is a distinct addition to the literature of the subject. It was, indeed, a pleasure to have been privileged to review this monograph which unquestionably falls in the latter class. In the short space of 260 pages, including the index, the author has succeeded in covering the embryology, anatomy and physiology of the stomach and duodenum, the diagnosis of lesions of these viscera, the preliminary preparation, anesthesia, incisions and after treatment. The illustrations, most of which are new, are well chosen and skilfully executed. The selection of the material presented has been done thoroughly, and, while one may occasionally not agree with every statement, there is behind them a wealth of clinical experience. The author has long been known as a surgeon who realizes the importance of function in the rehabilitation of patients with lesions of the stomach and duodenum, and in this volume he has time and time again referred to the necessity of the surgeon considering the physiology of this area if he is to obtain the best possible results. If the Reviewer does not interpret the work incorrectly, this monograph will soon become a standard by which subsequent volumes dealing with this subject will be judged.

I. R.

**THE ENLARGED PROSTATE AND PROSTATIC OBSTRUCTION.** By KENNETH M. WALKER, F.R.C.S., M.A., M.B., B.C., Jacksonian Prizeman and Hunterian Professor, Royal College of Surgeons, 1911, 1922, 1924, 1933; Lecturer in Venereal Diseases, St. Bartholomew's Hospital, etc. Pp. 223; 63 illustrations, 1 colored. Second edition. New York: Oxford University Press, 1933. Price, \$4.25.

A REEDITING of the 1926 publication was to be expected because of the recent important advances in therapy. The book keeps its attractive small size and is better printed than before. New chapters on Mechanism of Obstruction and The Malignant Prostate are incorporated. That on

Obstruction at the Bladder Neck is rewritten *in toto* to distinct advantage over the older edition, while the chapter on Per-urethral Operations is brought up to date by the addition of prostatic resection, on which the author is one of the recognized authorities in Great Britain. It is to be commended again for its concise presentation and sound judgment.

A. R.

ST. GEORGE'S, 1733-1933. By J. BLOMFIELD, O.B.E., M.D. Pp. 120; illustrated. London: The Medici Society, 1933. Price, 5s.

THE history of this important London hospital and medical school (the latter established a century later), which for 200 years has occupied its present site at Hyde Park Corner, is adequately covered in this compact little volume. Chapters for each half century of its existence, with lists of governors who have filled the office of treasurer, physicians and surgeons and their assistants, from 1733 on, complete the volume. It is perhaps significant of the continued dominance of the clinical side in London medical schools, that a consulting and honorary bacteriologist (both appointed in April, 1913) are the only non-clinical names included. John Hunter, of course, frequently appears in the earlier pages, while such familiar names as Abernethy, Acland, Allbutt, Askew, Baillie, Charles Bell, Brodie, Burdon-Sanderson, Cheselden, Michael Foster, Gull, Heberden, Home, Manson, Humphry Rolleston and Thomas Young remind us of the distinguished position that this institution has always occupied.

E. K.

HISTOPATHOLOGY OF THE PERIPHERAL AND CENTRAL NERVOUS SYSTEM. By GEORGE B. HASSIN, M.D., Professor of Neurology, University of Illinois, College of Medicine, and Attending Neurologist, Cook County Hospital, Chicago. Pp. 491; 229 illustrations. Baltimore: William Wood & Co., 1933. Price, \$6.00.

HASSIN's new work is the third text on neuropathology to be published in this country within the present year. It is a systematic description of the pathologic changes which may occur in the peripheral nerves, the spinal cord and the brain. The author has wisely refrained from extensive discussions of clinical features, since there are available a number of excellent books on clinical neurology. Nor is there to be found in this work a discussion of general pathology, for such concepts as inflammation, degeneration, trauma and tumor growth are well treated in our several modern textbooks on pathology. The book is concise and in fact as well as in name covers the subject matter indicated by the title. The illustrations are excellent. The book itself clearly reflects the long and distinguished career of the author in the field of neuropathology. The Reviewer would invite particular attention to the final chapters wherein is given a outline of the staining methods that are used in Hassin's laboratory.

B. L.

SOME MODERN EXTENSIONS OF BEAUMONT'S STUDIES ON ALEXIS ST. MARTIN. Beaumont Foundation Lectures. By W. B. CANNON, M.D., S.D. LL.D., George Higginson Professor of Physiology, Harvard Medical School; Beaumont Lecturer for 1933. Pp. 87. Detroit: Lectureship Foundation Committee of the Wayne County Medical Society, 1933.

THE twelfth series of lectures on this foundation coincide with the centennial of Beaumont's great work on the gastric juice. It is especially appropriate they should be given by one who is so well able to present recent important advances that are connected with the work of our pioneer physiologist. Beaumont's correct and false views on hunger and thirst, relations of digestion to health, and digestive disturbances produced by pain and emotional excitement are well reviewed and elaborated in the light of present knowledge.

E. K.

YOUR LONG-SUFFERING STOMACH. By ARTHUR F. KRAETZER, M.D. Pp. 120; illustrated. New York: Robert M. McBride & Co., 1933. Price, \$1.50.

THE author has crisply condensed much sound information on nutrition within the span of nine chapters. His advice to diners may be summarized in the Socratic phrase "nothing too much." There is little of the partisan in him and his common sense views should prove a timely antidote to the prevailing dietary fads. As a book primarily for laymen, it is properly somewhat arbitrary on points which, strictly speaking, may still be considered debatable. Finally, as is essential in this type of book, there is wit enough to season the more technical portions for the casual reader.

W. A.

SPONTANEOUS PNEUMOTHORAX IN THE APPARENTLY HEALTHY. By HANS KJAERGAARD. Pp. 251; 29 illustrations. Copenhagen: Levin & Munksgaard, 1932. (Translated from the Danish by Hans Andersen, M.D., Copenhagen.)

ON the basis of 51 cases coming under his own scrutiny, and some 200 cases reported in the literature, the author concludes that spontaneous pneumothorax in the apparently healthy is a distinct clinical entity, for which he suggests the term pneumothorax simplex. It includes all cases of spontaneous pneumothorax occurring without demonstrable cause in healthy persons without demonstrable tuberculosis, and running an afebrile course without any, or with at most trifling, pleural effusion. Due to the rupture of a valve vesicle on the surface of the lung, a vesicle arising either near a scar of a small healed tuberculous process or through local emphysematous changes without scar tissue, the condition may be assumed to have nothing to do with active tuberculosis and the patients should be spared unnecessary treatment for, and fear of, tuberculosis. The evidence presented is clear-cut and convincing.

R. K.

DISEASES OF THE NERVOUS SYSTEM. By W. RUSSELL BRAIN, M.A., D.M. (OXON.), F.R.C.P. (LOND.), Assistant Physician to the London Hospital and the Royal London Ophthalmic Hospital; Physician to the Hospital for Epilepsy and Paralysis, Maida Vale. Pp. 899; 50 illustrations. New York: Oxford University Press, 1933. Price, \$8.75.

SOME deviation is here shown from the conventional arrangement of this branch of medicine. Opening with a rather lengthy discussion of the anatomy and physiology, as applied to the interpretation of the physical signs of nervous diseases, the further consideration of these branches appears later as introductions to the clinical sections.

Encephalitis lethargica and intracranial tumors are treated in the full light of modern research. The much neglected subject of fibrositis is considered. The value of fixation of the muscles in Bell's palsy is recognized, though not in its most approved form. The immediate and late effects of head traumata are fully discussed. The importance of the recently discovered metabolic centers in the hypothalamus is carefully considered, including their relation to general medicine, and a new chapter appears, entitled: Diseases of the Nervous System in Relation to Life Insurance. No preference is shown for the various conflicting theories concerned with psychopathology, the reader being referred to the original works of such authors. Intelligence tests—and these should include survey of the emotional realm—have been relinquished to psychiatry, but both departments of neuropsychiatry are still claiming the psychoneuroses.

One finds here the recent advances, thus giving the most comprehensive neurology that has yet appeared in English, and its popularity is predicted. The subject matter is followed by an excellent reference list and index.  
N. Y.

**HEALTH AND ENVIRONMENT.** (Recent Social Trends Monographs No. 1) By EDGAR SYDENSTRICKER. Pp. 217; 50 illustrations. New York: Hill Book Company, 1933. Price, \$2.50.

ONE of the series of monographs resulting from the work of President Hoover's Research Committee on Social Trends, this book endeavors to cover the whole field of health and disease in relation to geographic factors, city and country, economic and social status and occupation, without forgetting the known influence of heredity. Mortality trends—both in their civic and genetic aspects—each receive separate chapter treatment. Necessarily concerned chiefly with statistical analysis, the book is of value rather as a permanent collection of important data than for casual light reading.  
E. K.

**LECTURES ON THE HISTORY OF MEDICINE, 1926-1932 (MAYO FOUNDATION LECTURES).** Pp. 516; 26 illustrations. Philadelphia: W. B. Saunders Company, 1933. Price, \$5.00.

HEREIN is produced a series of 18 lectures under the auspices of The Mayo Foundation and several midwest universities. As explained by Dr. Louis Wilson, in the Introduction, "No attempt was made to cover the entire field of medicine nor to present the topics in any logical sequence. Men of learning were invited to come at their own convenience and to talk on historical topics of their own selection." The topics naturally cover a wide range. The Physiology of Respiration, The History of the Day, Billings, Paré, First American Journals, The History of the Dance of Death and so on, by such well-known writers as Sewall, Coupal, Seelig, Garrison, Packard, Corner and others. The book should furnish many pleasant evenings to the literary minded and we are glad to note that there will be more to come.  
E. K.

## BOOKS RECEIVED.

### NEW BOOKS.

*Metabolic Diseases and Their Treatment.* By DR. ERICH GRAFE, Professor of Medicine and Director of the Clinic of Medicine and Neurology at the University of Würzburg, Germany. Translated by MARGARET GALT BOISE, under the supervision of EUGENE F. DuBOIS, M.D., Medical Director, Russell Sage Institute of Pathology, and Professor of Medicine, Cornell University Medical College; and HENRY B. RICHARDSON, M.D., Associate Professor of Medicine, Cornell University Medical College. Pp. 551; 37 illustrations. Philadelphia: Lea & Febiger, 1933. Price, \$6.50.

*Industrial Health Service.* By LEVERETT DALE BRISTOL, M.D., Dr.P.H., Health Director, American Telephone and Telegraph Company, New York City; formerly Commissioner of Health of the State of Maine, and Professor of Preventive Medicine and Public Health, University of Minnesota. Pp. 170. Philadelphia: Lea & Febiger, 1933. Price, \$2.00.

- Histology.* By S. RAMON-CAJAL, M.D. (MADRID), F.R.S. (LONDON), LL.D. (CLARKE), Director, Royal Cajal Institute for Medical Research; Emeritus Professor of Pathology, University of Madrid Faculty of Medicine; Nobel Premiate in Medicine; Life Senator of Spain. Revised by J. F. TELLO-MUNOZ, M.D. (MADRID), Professor of Pathology, University of Madrid Faculty of Medicine. Authorized translation from the tenth Spanish edition by M. FERNAN-NUNEZ, M.D. (MADRID), Professor of Pathology, Marquette University Medical School. Pp. 738; 535 illustrations. Baltimore: William Wood & Company, 1933. Price, \$8.00.
- Red Blood Cell Diameters.* By CECIL PRICE-JONES, M.B. (LOND.). Pp. 82; 44 illustrations. New York: Oxford University Press, 1933. Price, \$3.50.
- Diet and Dental Health.* By MILTON T. HANKE. Pp. 236; several illustrations; 21 graphs and 42 plates, mostly colored. Chicago: The University of Chicago Press, 1933. Price, \$4.00.
- Lectures on the History of Medicine, 1926-1932 (The Mayo Foundation Lectures).* Pp. 516; 26 illustrations. Philadelphia: W. B. Saunders Company, 1933. Price, \$5.00.
- Verhandlungen der Deutschen Gesellschaft für Kreislaufforschung. VI. Tagung. Gehalten zu Würzburg am 6. und 7. März 1933.* By PROF. DR. BRUNO KISCH, Cologne. Pp. 276; 97 illustrations and 35 tables. Leipzig: Theodor Steinkopff, 1933. Price, Rm. 15.—.

## NEW EDITIONS.

- Diseases of the Chest and the Principles of Physical Diagnosis.* By GEORGE WILLIAM NORRIS, A.B., M.D., formerly Professor of Clinical Medicine, University of Pennsylvania, and Chief of Medical Service "A," Pennsylvania Hospital; and HENRY R. M. LANDIS, A.B., M.D., Sc.D., Professor of Clinical Medicine, University of Pennsylvania, and Director of Clinical and Sociological Departments, Henry Phipps Institute of the University of Pennsylvania. With a chapter on The Transmission of Sounds Through the Chest, by CHARLES M. MONTGOMERY, M.D., formerly Physician to the Phipps Institute, Philadelphia; and a chapter on The Electrocardiograph in Heart Disease, by EDWARD B. KRUMBHAAR, Ph.D., M.D., Professor of Pathology, University of Pennsylvania School of Medicine. Pp. 997; 478 illustrations. Fifth edition revised. Philadelphia: W. B. Saunders Company, 1933. Price, \$10.00.
- A Text-book of Medicine.* By AMERICAN AUTHORS. Edited by RUSSELL L. CECIL, A.B., M.D., Sc.D., Professor of Clinical Medicine, Cornell University Medical College, and Associate Attending Physician, New York Hospital; Associate Editor for *Diseases of the Nervous System*; and FOSTER KENNEDY, M.D., F.R.S.E., Professor of Neurology, Cornell University Medical College, and Director, Department of Neurology, Bellevue Hospital. Pp. 1664; 30 illustrations. Third edition, revised and entirely reset. Philadelphia: W. B. Saunders Company, 1933. Price, \$9.00.
- A Practical Medical Dictionary.* By THOMAS LATHROP STEDMAN, A.M., M.D. Pp. 1256, with many text illustrations; 22 plates, 4 colored. Twelfth revised edition. Baltimore: William Wood & Company, 1933. Price, Plain Edge, \$7.00; Thumb Indexed, \$7.50.

Since 1908 this book has been quietly exerting its influence for better spelling and use of words. In this edition, about a thousand new words have been added, including a number of terms of the Nomenklatur Kommission (marked N K).



# PROGRESS OF MEDICAL SCIENCE

## ANNOUNCEMENT.

For sometime we have felt the inadequacy of monthly abstracts of isolated articles in attempting to cover the progress of medical science. We have also recognized that this method is being followed by the *Journal of the American Medical Association*, a weekly which is presumably taken by all our subscribers. We have, therefore, decided that, beginning with this number, longer reviews of important topics that have recently undergone considerable development will be presented by two departments each month. The same total space will be utilized as heretofore and each department will be represented twice annually. It is our hope that this plan will furnish our readers with more useful connected and digested information about medical progress than did the method we are abandoning. The recent discontinuance of *Progressive Medicine* makes this change especially timely. We shall be glad to forward to the appropriate Progress Editor any suggestions of desirable topics. [THE EDITORS.]

## MEDICINE

UNDER THE CHARGE OF

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## ANEMIA, DIET AND VITAMIN DEFICIENCY.

THE studies started by Whipple some years ago on the influence of various types of food substances upon the blood picture, and continued in the treatment of pernicious anemia by Minot, who had independently developed the use of large amounts of liver in this condition, have stimulated many in the last few years to study the effect of diet upon anemia in general, and more specifically the effect of diet on the more definite anemia entities. Such studies include those that have to do with the presence of some substance in food which, when lacking, has an influence upon the development of pernicious anemia, upon sprue and the pernicious types of anemia seen in pregnancy or those that have as their etiologic factor a definite vitamin inadequacy of the diet. Also has been the study of hypochromic anemia, which, it has been suggested, may depend upon either some deficiency in gastric secretion or on the inability of the gastro-intestinal tract to make use of those food substances which are ingested and which subsequently stimulate blood formation. Many of these studies have appeared in this journal. Only one needs be referred to briefly here. STRAUSS and CASTLE (AM. J. MED. SCI., 1933, 185, 539) come to the conclusion that the macrocytic anemia of pregnancy may be produced by the lack of the extrinsic factor, vitamin B<sub>12</sub>. This type of anemia can be relieved by liver extract, but in some instances supplementary iron rations must also be given. They suggest likewise that the hypochromic anemia of pregnancy is due to a direct dietary deficiency or is

one conditional upon gastric anacidity or associated defects, when the fetal demand for blood-bearing materials has to be met. This may be relieved by iron.

A relatively early communication of CASTLE and STRAUSS (*The Extrinsic [Deficiency] Factor in Pernicious and Related Anemias*, *Lancet*, 1932, 2, 111) advanced the hypothesis that there was an extrinsic factor lacking in pernicious anemia and other macrocytic types of anemia, which they believed to be a protein or a closely related substance. Further studies have lead them to believe that vitamin B<sub>2</sub> is the extrinsic factor, or at least a substance closely related to vitamin B<sub>2</sub>; furthermore, that these macrocytic types of anemia may be due to a lack of a specific hemopoietic reaction between the extrinsic factor (vitamin B<sub>2</sub>) and the intrinsic factor of the normal human gastric juice. In those cases of macrocytic anemia, such as sprue, the disease is due often to a lack of the extrinsic factor. They state, furthermore, that liver extract is rich in vitamin B<sub>2</sub>, which may explain the results of feeding liver extracts that occur when the extrinsic factor is lacking in sprue and the anemia is cured by this therapy.

This most fundamental and important work that has been done on the relation of pernicious anemia and related macrocytic anemias to vitamin deficiency has come from the Boston City Hospital under the stimulation of Doctor Minot. CASTLE (*The Etiology of Pernicious Anemia and Related Macrocytic Anemias*, *Ann. Int. Med.*, 1933, 7, 2), to whom was awarded, at the Montreal meeting of the American College of Physicians, in February, 1933, the John Phillips Memorial Prize for the best clinical experimental work produced in the year, summarizes in his address succinctly and clearly the explanation of why certain cases of macrocytic anemia will respond to liver extract and to yeast and others only to liver extract. To quote Castle: "The difference appears to depend on the presence or absence of the intrinsic factor. In the light of this evidence it is clear that the common factor for producing macrocytic anemia is the failure of the specific reaction between the extrinsic and the intrinsic factors. These anemias should, then, occur both where, on the one hand, the diet is deficient in vitamin B<sub>2</sub>, and on the other hand, where, although the diet is not grossly deficient, lack of the intrinsic factor is found. Thus, sprue and the macrocytic anemias of the tropics occur in communities or in individuals partaking of defective diets and show gastric anacidity less commonly than is found in patients with Addisonian pernicious anemia, who usually have more normal diet habits. In many cases a combination of gastric defect and dietary deficiency may exist, which would have the same result upon the specific hematopoietic reaction as a total absence of either of its components.

"If the evidence be valid that the extrinsic factor or the specific hematopoietic reaction with normal human gastric juice is vitamin B<sub>2</sub>, a new concept of the relation of certain vitamins to the conditions caused by their lack would seem to be involved. The action of a vitamin in curing a deficiency may thus be essentially dependent upon a specific process in the gastro-intestinal tract; and the deficiency state not so much a deficiency in the diet as a deficiency of a reaction in the gastro-intestinal tract or elsewhere in the body."

Another aspect of vitamin B deficiency is exemplified by the studies of FOUTS, KEMPF, GREENE and ZERFAS (*Vitamin B Intravenously for*

*Treatment of Neurologic Changes in Pernicious Anemia*, J. Indiana Med. Assn., 1932, 25, 448). Their study was instituted because of the many conflicting reports in the literature of the effect of oral liver treatment when central nervous system involvement occurs in pernicious anemia. In this article, a long list is given of those who have had favorable results and an equally long list is given of those who have had unfavorable results in the treatment of the neurologic complications of pernicious anemia. In some instances, even an increase in the neurologic symptoms has been reported to take place in the course of liver therapy. These authors prepared a concentrated extract of vitamin B, containing mainly the B<sub>1</sub> factor and little of the B<sub>2</sub>, an extract potent in the curing and relieving of the polyneuritis of pigeons. These patients with pernicious anemia were given the extract for a period varying from 1 to 7 months, without any improvement in their neurologic expressions.

In addition to the studies that have been made on the hemoglobin and red cell content of the blood when the diet lacks vitamin B, SURE and BUCHANAN (*Influence of Deficiency on Differential Leukocyte Count of Albino Rat During Lactation*, Proc. Soc. Exp. Biol. and Med., 1932, 30, 174) have studied the leukocyte counts in the presence of a deficiency of this vitamin. There develops a relative lymphopenia and a corresponding leukocytosis in the lactating albino rat. A specific deficiency was implied in that in the majority of the instances there was a great loss of weight associated with inanition.

In a purely clinical paper (*Three Cases of Chronic Dietary Deficiency*, Med. Clin. North America, 1933, 16, 761), MINOT discusses the symptoms of fatigue, anemia and prolonged coagulation time of the blood which occur when individuals are on a diet that is nutritionally deficient. He insists that successful therapeutic results will be obtained only by a suitable way of living, including the taking of food properly and an optimal diet for the individual patient.

Another phase of the anemias due to nutritional faults is represented by numerous studies that have been made with various types of food substances. In one of these (*A Preliminary Report on the Cure of Nutritional Anemias by One of the Legumes*, Am. J. Trop. Med., 1933, 13, 327), COOK and RIVERA studied in Puerto Rico, where the diet of the poor is restricted and monotonous and anemia is common, the potency of the native pea in hemoglobin formation, reviewing notably the work of Hart and Steenbock, who have studied many types of food substances in the control of anemias of a nutritional nature. These observers put rats upon a standard anemia-producing diet. They were then fed a particular pea, the pigeon pea. It was found that these peas exhibited curative properties in the native rat, the fresh peas showing greater regenerative power than did the ash of the equivalent quantities when they were both fed at levels suboptimal to induce normal regeneration. Their experiments demonstrate to the satisfaction of the investigators that there is higher efficiency in blood formation in fresh foods than in inorganic elements.

A very comprehensive study of the nutritional anemias of infancy and early childhood has been presented by PARSONS (*Arch. Dis. Child.*, 1933, 8, 85). This work is a most thorough clinical and experimental presentation. The paper is divided into several subsections, of which

those germane to the present discussion include a report on the effect of yeast on nutritional anemias in rats. Yeast is rich in vitamin B complex. It contains also iron, both in the organic and inorganic forms, copper and two important caseins, cerevisine and zymocasein. Feeding this yeast to the standard anemic rat, their results were comparable to those who have done similar experiments. The anemia was quickly controlled. In order to do away with the possibility that the copper and iron of the yeast might account for its anemia-relieving properties, a yeast preparation was made with the least possible copper, iron and manganese content. This yeast produced a cure of the anemia, although more slowly than by the other methods, such as the addition of a small amount of iron, which resulted in the formation of more hemoglobin than in the so-called anemic yeast of this author. The next step that was taken, to determine if possible what was the curative factor in yeast, was to give a watery extract of this substance which would contain the vitamin B content and the amino acid salts, but no hematin. Again a cure resulted which was satisfactory. Their experiments allowed them to state that yeast has a curative effect upon the nutritional anemia of rats and allows reproduction to take place. Yeast is more effective when added to a milk diet than copper or iron, judging from the standards based on growth, but it is not a complete supplement. The addition of yeast and iron to milk completely rectifies the diet and overcomes the anemia. They believe that the B complex has a definite influence on hematopoiesis, but that it cannot be regarded as an effective curative agent. The authors are not able to make a categorical response to the questions they have propounded. They do suggest that the results that were achieved are due in part to the iron and copper present in yeast, as well as the vitamin B complex and possibly to amino acids. The clinical studies were carried out on nutritional anemia, the anemias of prematurity, scurvy and celiac disease in a group of infants. Yeast therapy was tried in view of the results that were achieved in the rat experiments. It was found that the yeast was less effectual in the treatment of the nutritional anemias of childhood than in the rat. The anemia of scurvy was very promptly cured by adding orange juice to the diet without any other medication and while the child was on a milk diet. The anemia of celiac disease, from their experiments, was due largely to the absence of Castle's intrinsic factor. The anemia was not relieved by the extract of marmite, which would supply vitamin B complex, although Castle and Rhoads state that in sprue and celiac disease there is at times a lack of the extrinsic factor which can explain the anemia.

SCOTT and DELOR (*Nutritional Anemia, Ohio State Med. J.*, 1933, 29, 165) fed to the white rat, suffering from nutritional anemia, milk obtained from a Holstein herd fed with warm hydrolyzed alfalfa hay and grain. Another group of animals were fed an iron and copper-free extract of alfalfa and the diet of a third group was augmented by the addition of a liver oil high in vitamin A. They mention the work of Guha, who thinks that both milk and yeast contain a factor that is required for the normal growth of rats which is different from other known vitamins. These experiments, as well as preceding ones, suggest that vitamin A is essential for normal blood regeneration and that vitamin A can cure certain types of nutritional anemias.

Still another paper, based on the work of Steenbock and Hart, is

that of FARMER and CORY (*Hemoglobin Regeneration of Anemic Albino Rat With Dietary Supplements of Spinach, Apricot and Liver*, *Proc. Soc. Exp. Biol. and Med.*, 1932, 29, 766), who supplemented the daily rations of rats on the standard anemia diet with spinach, apricot or liver. They noted that the puréed spinach or apricot gave a greater hemoglobin response than did the non-puréed material or the ash. The hemoglobin building ratio of these three foodstuffs is comparable to that achieved in the rats of Robschheit-Robbins which were rendered anemic by bleeding. In their rats, Farmer and Cory found that these food substances, liver, apricot and spinach, can be graded in a ratio of 4-2-1.

BEEBE and WINTROBE (*Effect on Idiopathic Hypochromic Anemia of Beefsteak [Hamburger Steak] Digested With Normal Gastric Juice*, *Arch. Int. Med.*, 1933, 52, 464), in discussing idiopathic hypochromic anemia, state that the most generally held opinion is that the anemia depends upon some gastric secretion deficiency or depends upon dysfunction of the absorptive properties of the gastro-intestinal tract. They repeated Castle's original experiments with pernicious anemia patients, beefsteak properly digested with normal gastric juice being fed to their patients with hypochromic anemia. Five individuals were given 200 gm. of beefsteak digested with 100 cc. of normal gastric juice. In no case was there the expected reticulocyte rise, and there was no increase in hemoglobin, in the value of packed red cells and in the red blood count. It would seem to these investigators that in this type of anemia a specific substance is not lacking, and this, despite the fact that in idiopathic hypochromic anemia there occurs an achlorhydria.

An interesting series of papers comes from the Rochester school, as a continuation of Whipple's previous important work. The fifth paper of this new series, by BOGNIARD and WHIPPLE (*The Iron Content of Blood-free Tissues and Viscera*, *J. Exp. Med.*, 1932, 55, 653), is interesting because the Rochester investigators find that there is a large reserve store of iron in the liver, spleen and marrow which may be modified by diet. The reserve store of iron may be depleted by an anemia period of 2 to 3 months.

This review is of some of the work only that has been done in the past year in linking up anemia with nutritional faults and dietary inadequacy of vitamin. It is known that anemia may have a different and varied etiology; that dietary errors, be they lack of protein, mineral elements or vitamins, are a very common cause of anemia. Indeed, so frequent are these types of anemia that OTTENBERG (*Reclassification of Anemias*, *J. Am. Med. Assn.*, 1933, 100, 1303) suggests an etiologic reclassification of the anemias into three broad divisions: (a) The deficiencies, (b) direct injury to the blood-making organs, and (c) blood destruction from any cause. Fundamentally the anemias due to vitamin deficiency are closely interwoven and definitely related in that one or another of the vitamins is either lacking in the diet or cannot be utilized by the body. Thus, one type of nutritional anemia may develop as a result of inadequacy of vitamin A; the anemia of scurvy can be cured with vitamin C; but, although vitamin B (or B<sub>2</sub>) inadequacy has a definite influence on the development of the macrocytic types of anemia, the explanation of the mechanism of production of this type of anemia differs somewhat from the anemias that are produced by deficiency in other vitamins.

## PEDIATRICS

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UNDER THE CHARGE OF  
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OF PHILADELPHIA.

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### POLIOMYELITIS—A SURVEY OF RECENT CONTRIBUTIONS.

In a review prepared more than a year ago (*J. Pediat.*, 1932, 1, 358) SCHULTZ stated: "Though we may claim to a certain degree of enlightenment as to the cause, nature and effect of poliomyelitis, we are still in the 'thesis stage' of our knowledge of this disease." Since the preparation and presentation of the above paper there have been in different parts of the country outbreaks of this disease, in some localities amounting to severe epidemics. As a consequence much material has been available for the observation and study of the different phases of the disease. Notwithstanding it is a question whether or not the many contributions on the subject have actually contributed any material advance to our knowledge. It would be impossible here to abstract all or even many of these papers, and where some may be abstracted more or less at length, the criterion for dwelling on one presentation rather than another has been the impression made upon the Reviewer rather than the ultimate scientific valuation.

From the standpoint of epidemiology SCHULTZ (*Loc. cit.*) reminds us that it is well established that this disease is spread chiefly, if not entirely, by the dissemination of nasopharyngeal secretions of virus carriers, the virus having been demonstrated in the mucous membranes of the nasopharynx, not only during the acute period of the disease, but also in some cases several months after convalescence. The virus has been demonstrated also in the nasopharyngeal washings of healthy individuals who have been in contact with patients. He also says that the disease may be acquired by means of the milk, but he stipulates that when man acquires the disease by drinking contaminated milk, the infection most likely results from a contact of the virus-contaminated milk with the nasopharyngeal vault, rather than by a passage of the virus from the intestinal tract to the central nervous system by some more or less indirect route. He adds that milk can never act as a culture medium, as in the typhoid-contaminated milk, but merely as a mechanical vehicle of the virus, and it is possible that either food-stuffs might play a similar rôle as a vehicle for the virus from a "virus-carrying food handler" to a new host.

Paralleling this thought we find TOOMEY and AUGUST (*Am. J. Dis. Child.*, 1933, 46, 262) making a comparison between the epidemic peak and the harvest peak in the neighborhood of Cleveland. They stated that infantile paralysis need not be due necessarily to fruits and the like, but perishable foods might serve as one of the vehicles by which the disease is carried. Such a concept would explain the somewhat explosive and dispersive type of infection that they observed during the harvest peak. They point out that the handling of infected fruit or vegetables, the contamination of fruit and vegetables by infected

persons, the eating of infected fruits and vegetables by cattle with subsequent infection of the milk, and the spreading of the infection from fruit to fruit by flies might explain at least one mode of transmission and the increased incidence at this time of the year.

From the etiologic aspect, it is now recognized that the infection manifests itself in adult life with more frequency than was formerly thought. This has been emphasized by the rise to prominence of our President, Mr. Roosevelt, who suffered his infection in his thirties. Another well-known case is that of Dr. Walter Stewart, of Atlantic City, who reports his case as quoted later. Schultz comments on the experimental attempt of Jungeblut and Engle, in 1931, to show that resistance to poliomyelitis in adults may be determined by the internal secretions, especially by the glands determining sexual maturity. Schultz questions why the incidence of adult's immunity in a rural district was found by Aycock and Kramer to be less than half the incidence of immune persons in an urban community. This is an argument against the theory of sexual retardation, as there is nothing to indicate that persons living in the country are less well developed than those living in cities. However, it is much more plausible to assume that the immunity results from virus contact, a more likely occurrence in the city than in the country. Immunity may be total, partial or relapsing. Many children and most adults have an acquired if not a natural immunity. In others, there is an incomplete immunity as evidenced by what has been termed, recently, abortive forms of poliomyelitis. To speak of another form of incomplete immunity as relapsing may be a misnomer, as this may be seen in partial immunity with sudden exposure to infection of excessive virulence. The two latter types are well illustrated in the report of STEWART (*J. Pediat.*, 1933, 2, 393), who for 6 weeks was in contact with 35 various cases of poliomyelitis in the isolation hospital. His first child became infected 7 days before the seizure of the father. It would seem that the father was a carrier for some time prior to the penetration of his own resistance. The first child to become ill passed through a typical illness without the development of paralysis; the second was seized with the prodromal manifestations 2 days after the first. She ultimately developed paralysis of an upper extremity. The third became ill about the same time with an abortive attack. The father became ill 7 days after the first child and developed moderate loss of power of the lower extremities. The mother of the children showed the symptoms of the mild abortive type with no residual paralysis. In this family the father's blood was Group IV (Moss), the mother was Group I and the 3 children were all Group II. This report is of more than ordinary interest as the observations were made by 1 of the patients, who has had the advantage of the best training in pediatrics.

Season may play a part. TOOMEY and LIPSON (*J. Pediat.*, 1932, 1, 739) studied the influence of season and other factors in the incidence of poliomyelitis. They found that the morbidity curve for this disease showed that the majority of cases occurred during August, September and October in the vicinity of Cleveland. Ordinary factors associated with seasonal changes, such as temperature, dryness, increased precipitation, sunshine and the like did not seem to have any effect upon the case morbidity rate of infantile paralysis. There was a decrease

in precipitation and a normal or increased temperature curve in all but one of the epidemic years.

Regarding blood grouping in poliomyelitis, SHAW, THELANDER and KILGARIFF (*J. Pediat.*, 1932, 1, 346) present the observation on a group of 100 cases checked with 100 controls. Incidentally it is of interest to compare the results of blood grouping in the Stewart family with the results of this study. It is seen that the higher frequencies are noted in Groups IV and II with few or none in Group I, which was also noted by Grooten and Kassovitch and others. Further study is required on the frequency of incidence and relative severity of the infection in the Moss blood groups. If the findings so far made are borne out in large numbers of cases observed, an aid to diagnosis may be developed as well as a criterion for prognosis. It is conceded universally that early diagnosis is of the utmost importance in permitting early specific treatment. While some question has been raised about the efficacy of serum therapy by some observers, even these for the most part admit that the earlier the therapy is administered the better are the results.

ROSENBERG (*J. Med. Soc. New Jersey*, 1933, 30, 248) describes the onset of the illness: "The child rapidly becomes feverish and drowsy. In most cases this drowsiness becomes an outstanding symptom. The patient can be aroused easily from this stupor but, when awakened, is strikingly irritable and restless. He particularly does not want to be annoyed, and just as soon as he is left alone relapses into a comatose state. The mind is clear despite this drowsiness, and if the child's coöperation can be engaged, he will complain of two significant symptoms—occipital headache and pain in the back. Starting to examine the patient, the physician may or may not have poliomyelitis in mind, but he will suddenly get the lead as he observes the movements of the child. When he must ask the patient to sit up or turn over, it becomes evident immediately, as the child responds, that there is disinclination to flex the spine, and as the attempt is made to assume the upright position, he extends his arms and rests on his arms placed far behind his back. If the patient should now be asked to fold his arms, he will reluctantly try and quickly revert to his original position. The characteristic posture of supporting himself that the child takes is known as Amoss' sign. If asked to turn over on his abdomen, it will be evident that the movement is painful, and while he is turning it may be noticed that the spine is held straight and stiff as a poker-back." Rosenberg points out that this may be further demonstrated by having the child standing and attempting to touch his toes, without bending his knees. In a true case of poliomyelitis this is impossible. It may be done partially in the early stages of the disease. The back is held rigid and all motion is at the hips. This resistance to anterior flexion is called the "spine sign." The Kernig sign is indeterminate. Other helpful signs and symptoms are enumerated. Stiffness and pain in the back of the neck are early signs. A distinct tremor of the fingers has been noted. This is supposed to be due to irritation of the anterior horns before degeneration has developed. Hyperesthesia is another early and prominent symptom. Tenderness along the spine and down the legs may be present. Muscular pain and twitchings are commonly located in one or more groups of muscles. There is an excessive response



to the patellar reflex early. Gastro-intestinal symptoms are usually seen early in the disease. They may be so marked as to give the impression that this is the only cause for the temperature. Sweating is very common, especially in the severer cases. The eyes show significant changes, such as glazing of the sclera and cornea, and there is circumorbital puffiness. In other infectious diseases the eyes are bright and shiny. The pre-paralytic stage lasts in most cases for 4 days. If there is no paralysis by the 8th day there is little danger of its occurrence. Diagnosis in this stage may be difficult, because all cases do not run the typical course. Rosenberg points out that the most valuable symptoms in the pre-paralytic stage are those referable to the spine: occipital headache, poker-back attitude, resistance to motion of the spine and hyperesthesia of this region. Diagnosis is usually cleared by spinal fluid examination. GONCE (*Journal-Lancet*, 1932, 52, 548) says that the spinal fluid pressure may or may not be increased. The fluid may be clear, where the cell count is still low, or hazy, or have a ground-glass appearance in the presence of a high concentration of cells. The number of cells averages from 200 to 300, but the variation may be as great as from 20 to 1200 or more. The examination of the cells should be made within an hour as the cells tend to disintegrate. Albumin and globulin are moderately increased. The sugar may be normal or slightly increased. In the presence of epidemic, the diagnosis is usually made in even the atypical and mild forms. In sporadic cases it is easily possible to err if the case is not typical in its clinical picture.

A recent interesting study of the pathway of invasion as determined by the localization of the virus during the pre-paralytic stage was made by FABER (*Am. J. Dis. Child.*, 1933, 46, 680): "With an improved technique for intranasal inoculation of monkeys with poliomyelitis virus, the pathways followed by the virus from the nasal mucous membrane into and through the central nervous system and the approximate rate of invasion were determined. It was found that about four days were required for the virus to appear in detectable amounts in the central nervous system and then only in the olfactory bulb. By the fifth day it had spread to the hypothalamus and medulla, but it was not found elsewhere. On the sixth day it was present in the olfactory bulb, hypothalamus, midbrain and medulla, but not elsewhere in the brain or spinal cord. On the seventh day it was found for the first time in the spinal cord and spinal ganglions. This rather slow spread by continuity from a definite and sharply localized initial focus through the brain stem to the cord, with the avoidance of contiguous structures in the end brain and cerebellum, shows that the propagation of infection in poliomyelitis is not through the blood or the cerebrospinal fluid, but through the axons of the nerves, as previously demonstrated by Fairbrother and Hurst. As the inoculations correspond with the natural portal of entry in man, the inference is made that the route of invasion found in monkeys corresponds with that in man. If this conclusion is correct, the concept of the human disease as consisting of a preliminary stage of systemic, extraneuronal infection followed by invasion of the central nervous system through a hypothetically damaged 'meningohoroid barrier' is no longer tenable. The origin of some of the characteristic symptoms at the onset of poliomyelitis in man can, it is

believed, be traced to certain areas in the hypothalamus, thalamus and elsewhere in the brain stem which the virus traverses and infects, at least transiently, during its passage toward the spinal cord. A tentative classification of symptoms in chronologic order of development is offered, the clinical disease being divided into four successive phases: (1) The cerebral or diencephalic phase; (2) the phase of posterior poliomyelitis; (3) the phase of anterior poliomyelitis; (4) the phase of recovery. The advance of the disease may cease at the end of Phase 1 or Phase 2, giving rise to the so-called abortive type of poliomyelitis."

During the epidemics we are confronted by the demand of parents to undertake measures to prevent their children from developing the disease. A great many measures were taken during the late epidemic, and many children were injected with different materials. CARPENTER, STOKES and WOLMAN (*Am. J. Dis. Child.*, 1933, 46, 681), in a paper dealing with their experiences in immunizing against poliomyelitis, state: "During the epidemic of poliomyelitis in Philadelphia in the summer of 1932, an effort was made for widespread prophylaxis against the disease by passive immunization. So far as we are aware, such a procedure on a large scale has not been attempted previously. Six hundred and twenty children, under 10 years of age, residing in a carefully investigated census area where the disease incidence was highest, were given intramuscular injections of 66 cc. of parent's whole blood at the Children's Hospital of Philadelphia. Three mild cases of poliomyelitis without paralysis appeared in this group, an incidence of 1 in 207, whereas, according to the statistics of the Bureau of Health, the incidence of the remaining children in the same area in the same age group during that period was 1 in 640." In 721 children living outside the census area getting similar injections, 3 mild cases developed. Of 838 other children receiving blood or serum in various amounts, so far as we can determine, none subsequently had poliomyelitis. "The ages ranged from 1 to 15 years, although the large majority were under 11 years. The incidence in this entire number of 2179 children was 6 cases, or 1 in 363. In the city as a whole, of an estimated population of 289,500 children under 11 years of age, 521 cases of poliomyelitis occurred, an incidence of 1 in 555." From an undetermined number of prophylactic injections of various kinds variously given, data were collected on 11 children, who developed the disease. "In 1 child, severe paralysis of both legs developed, in another, moderate paralysis of one extremity, and in 2 others, slight transient weakness of one extremity. The remainder had no paralysis or weakness, and there were no deaths. Considered as a group, these children had a favorable course as compared with the rest of the children with this disease in the city, for of the 687 cases in Philadelphia, paralysis developed in about 70 per cent, and the mortality rate was 11.5 per cent. The blood of the donor for the child who was paralyzed in both legs was found to fail to neutralize a 5 per cent suspension of Philadelphia virus. The other child who was paralyzed received but 8 cc. of pooled convalescent serum. Although the series of cases is small, we believe that the data suggest that passive immunization by means

of adult or convalescent blood or serum is of value as a prophylactic measure against anterior poliomyelitis."

There exists a difference in opinion as regards the value of the active treatment of this disease by serum therapy. It is agreed, however, that serum therapy, if effective at all, must be administered early in the illness. PARK (*New York State J. Med.*, 1933, 33, 91) states that it is now definitely known that poliomyelitis is due to a filterable virus. He feels that this is of great importance, as there is no other disease due to a filterable virus that can be benefitted by an antiserum after clinical symptoms have developed. He refers to the studies made by Kraemer and Aycock during the 1931 epidemic, where, in better controlled experiments than any previously made, there was no statistical evidence that convalescent serum was effective. However, the opposite conclusion, that it was of no value, could not be drawn. In order to test the comparative value of the different methods of giving the serum, Park administered it to some of the patients by the Aycock method of combined intraspinal and intravenous injections, and by the Canadian method of subcutaneous injections. He also treated a number of patients by the intravenous method alone or combined it with the intramuscular injection. He varied the total dose from a minimum of 25 cc. to a maximum of 100 cc. Those persons treated in the first day of their meningeal symptoms showed somewhat better results than those treated later in the illness. However, in some cases even those treated later showed surprisingly good results, and on the other hand there were some good results in the untreated patients. It was observed that the route made no appreciable difference in the outcome. Those who received it intramuscularly developed in a larger percentage of cases some weakness, yet this was of very mild form. There seemed to be little or no statistical evidence of any difference between the serum treated and the untreated patients with pre-paralytic poliomyelitis based upon the studies of the Poliomyelitis Committee of the Academy of Medicine of New York City. The slight difference in favor of the untreated patients probably may be attributed to the accidental inclusion of a somewhat larger number of graver cases in the treated group. Park points out that statistically there was no evidence that the serum did any good, nor was there any evidence that it did any harm. The results of these controlled investigations indicate that in epidemics only a portion of the cases should be treated with serum, and the untreated cases should be observed with equal care, so that finally a conclusion may be reached as to whether the serum has any value at a time when the spinal cord is already invaded by the virus of poliomyelitis.

This viewpoint regarding serum therapy of poliomyelitis has been taken by a number of recent authors. WESSELHOEFT (*J. Pediat.*, 1933, 3, 330), SMELIE (*Arch. Dis. Child.*, 1933, 8, 75) and PETTE (*Deutsch. med. Wchnschr.*, 1933, 59, 873) are a few of those who agree with Park and Aycock and Kraemer. SHERMAN (*Deutsch. med. Wchnschr.*, 1933, 59, 1332) gives us the results of a variation of the methods of serum therapy. He reports treating 55 patients having acute anterior poliomyelitis by means of convalescent serum. He used the intraspinal and the intramuscular methods with doses of from 50 to 100 cc. Not get-

ting satisfactory results, he began transfusion of blood from convalescent patients. He based this change upon the fact that the blood is fresh and unchanged, and that it could be given in larger quantities than the serum, and because there is a possibility that the protective power of the whole blood is greater than that of the serum. This treatment was given to 71 cases (from 150 to 400 cc.). The transfusions were found to give much better results than the serum therapy. Not only were the mortality rate and the frequency of paralysis lowered, but on the course of the fever and on the general symptoms of the acute infection were lessened. He advises that records be kept of suitable donors for use in subsequent outbreak.

The cases that develop paralysis comprise what may be called the chronic group. In the slight cases prolonged rest, massage and modified electrical treatments may result in a more or less complete restoration of function. Basically, however, the slight, as well as the severe, forms become orthopedic problems. Many contributions to the literature of this phase of the disease are found. WHITMAN (*New York State J. Med.*, 1931, 31, 1397), TODD (*Lancet*, 1932, 223, 1044) and RYERSON (*J. Am. Med. Assn.*, 1933, 101, 1376) are a few contributors to the problems of the chronic stage. BOORSTEIN (*Med. J. and Rec.*, 1932, 135, 27) is cited because of his recommendations for the orthopedic treatment during the acute and convalescent stages. RUHRAH (*J. Pediat.*, 1933, 3, 217) gives the treatment of poliomyelitis both past and present. In his paper he deals with the history of the disease, but in concluding his presentation he summarizes the chief points. While his summary is rather general in character, it so well epitomizes the postparalytic care that it is quoted in full: "(1) The tendency is to recovery, much of the permanent paralysis is due to neglect or improper management. (2) Contractions and deformity can be avoided. (3) The principal thing in the treatment is rest, with the body recumbent, but in the position it would be in if standing erect. (4) The most important muscles should be favored early and until their recovery is assured. (5) Special adjustments of splinting must be made to favor muscles which should have it. (6) Fatigue, general and local, should be avoided. (7) Weight-bearing should not be allowed as long as recovery is expected. (8) Especial care should be taken not to allow at any time any stretching of affected muscles. (9) When recuperation is well established, carefully supervised exercise within the capacity of the muscle is of value. (10) Warm salt baths, very gentle massage (only after all tenderness has disappeared), fresh air and sunlight and warmth are valuable adjuvants in the treatment. (11) The splints or braces should be inspected frequently and changed to suit conditions. (12) The transition to weight-bearing should be gradual, avoiding overexertion and fatigue. (13) After all the improvement has been obtained that can be looked for as judged by a failure to improve under proper management, the patient should be gotten on his feet, using such apparatus as may be necessary. Old and neglected cases will need orthopedic care to correct deformity and exercise to develop latent muscle power. (14) Every case should be treated individually and not by any fixed routine. Changes should be made to suit conditions as they arise and deformities due to lack of balance of muscles carefully avoided."

## PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF NOVEMBER 20, 1933

**Zinc Hydroxid Powder as a Precipitant in a Simplified Procedure for the Preparation of Protein-free Filtrate of Blood.**—T. V. LETONOFF (Laboratory of the Division of Metabolism of the Philadelphia General Hospital). In connection with work on a method for the micro determination of chlorid in blood and plasma, it was necessary to employ a simple protein precipitant that would remove purins and yield a neutral filtrate. Various available procedures for removal of proteins were tested, but none were found satisfactory. In trying various substances, powdered zinc hydroxid was found to remove protein from diluted blood.

Trial of this substance indicated that it possessed many advantages that recommended its more general application in place of other protein precipitants. It was found that the use of powdered zinc hydroxid offered all of the advantages of the Somogyi procedure, yet eliminated the need for standardized solutions of sodium hydroxid and zinc sulphate. Only traces of zinc appeared in the filtrate. In most methods of precipitating proteins, considerable quantities of the reagents are present in the filtrate. Saccharids were removed completely, so that the level of true fermentable sugar could be determined directly by alkaline copper reagents. The filtrates are neutral and may be used also for urea nitrogen, non-protein nitrogen, creatinin, and creatin determinations. It is believed that this procedure may have useful application in biologic chemistry.

**Studies on the Mechanism of Sulphur Oxidation.**—JAMES C. ANDREWS and KATHLEEN C. ANDREWS (Laboratory of Physiological Chemistry, University of Pennsylvania). Although it is commonly assumed that the metabolic oxidation of cystin to inorganic sulphate involves the formation of a sulphonic acid such as cysteic acid, the great stability of this latter compound makes it difficult to explain its decomposition to give inorganic sulphate. It has been found impossible to obtain sulphate from cysteic acid under any conditions resembling those *in vivo*, and its administration to animals by other investigators has not caused increased excretion of inorganic sulphate.

The authors have investigated properties of certain cyclic sulphonic acid derivatives of cystin, such as cysteic acid hydantoin and cysteic acid phenyl hydantoin. These compounds are very unstable, and on neutralization with dilute alkali at ordinary temperatures they yield inorganic sulphate directly. The phenyl derivative yields about 15 per cent of its sulphur as inorganic sulphate, the simple hydantoin about 10 per cent. Other evidence points to two simultaneous methods of decomposition, one involving loss of  $\text{H}_2\text{SO}_4$  and the other involving a split in the hydantoin ring, producing an open chain compound, the sulphur of which remains stable as the sulphonic acid.

A further study of the mode of decomposition of these and similar cyclic sulphur compounds is planned by the authors.

**Relation of Nerve Regeneration to Contractility of Arterioles in the Rabbit's Ear.**—E. R. CLARK, E. L. CLARK and R. G. WILLIAMS (Laboratory of Anatomy, University of Pennsylvania). In the new tissue which grows in the space left in the "round table" chambers inserted in the rabbit's ear, there occurs a growth and differentiation of definite arterioles, capillaries and venules, the exact ages of which may be recorded photographically. Some of the arterioles develop a very definite power of contraction and dilatation, while others do not develop active contractility. There may also occur a growth into the chamber of a variable number of nerves. These, if non-myelinated, can rarely be seen without the use of vital staining. However, by an adaptation of the use of methylene blue, temporary staining of the axones has enabled us to see the non-myelinated nerves.

By combining the two methods, namely, by watching and recording the extent of definite contractions, and subsequently staining and recording the nerves, we have succeeded in demonstrating, on three successive stages in the same animal, at 10- and 9-day intervals, the progressive and coëxtensive side-by-side development of definite contractility in a newly forming arteriole, and of newly formed non-myelinated nerves; there were no nerves along arterioles which failed to show contractility. The contractions of the artery are considered to be the result of impulses reaching them through the nerves, since they occurred simultaneously with contractions of the original arteries of the ear whose nerve supply was undisturbed, contractions which could be brought about with ease by startling the rabbit either by a noise or some mechanical disturbance, while other arterioles along with all capillaries and venules showed slowing of blood flow, but no appreciable change in caliber.

The ages of the successive portions of the arteriole at the time of the inauguration of active contractility varied between 8 and 26 days. Ages of arterioles at the commencement of contractility in the other chambers have varied from 9 days to  $7\frac{1}{2}$  months.

The rate of growth of the nerves and of the extension of contractility in the arteriole dropped from an average of 70 micra per day during the first 10-day period to an average of 28 micra per day during the succeeding 9 days.

These observations prove that the nerves which control the contraction of muscle cells on arterioles may undergo new growth at the periphery in the adult animal, and may establish nerve control over vessel contraction.

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**The Nature of the Osmotic Effect of Solutions of Non-electrolytes on the Erythrocyte.**—M. H. JACOBS (Laboratory of Physiology, University of Pennsylvania). It has been known for many years that the erythrocyte swells less and is less easily hemolyzed in hypotonic solutions of non-electrolytes than in those of electrolytes of the same osmotic pressure. The most generally accepted explanation of this apparent anomaly is that in non-electrolyte solutions the internal osmotic pressure of the cell is more easily lowered by a loss of salts to the surrounding medium. Experiments by the hemolysis method, carried out with the assistance of Dr. A. K. Parpart, indicate that while an escape of salts from the erythrocytes of the ox into a surrounding sucrose solution

undoubtedly occurs in experiments of sufficiently long duration, this change is much less striking than an earlier one of a different nature, which begins almost instantly and is practically complete within a few minutes. The initial change, which unlike the later one is readily reversible, is believed to be due to an exchange of anions from the cell for hydroxyl ions from the solution, the resulting increase in the base bound by hemoglobin causing a decrease in the osmotic pressure of the cell contents. Calculations indicate that the expected osmotic effect of such an ionic shift is of the order of magnitude of that actually observed.

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**Effect of Adrenalectomy on Salt Metabolism in Rats.**—MITCHELL I. RUBIN and ELIZABETH T. KRICK (Laboratory of Department of Pediatrics, University of Pennsylvania; Children's Hospital of Philadelphia). Studies on the salt metabolism following a complete bilateral adrenalectomy in white rats were presented.

Balance studies of calcium, magnesium, sodium, potassium, phosphorus, chlorine and nitrogen were made before and after adrenalectomy. It was found that during adrenal insufficiency there was a marked loss from the body of all elements studied; so that in most instances a negative balance resulted.

A salt mixture solution containing a combination of the chlorides of calcium, magnesium, sodium and potassium was used to treat these animals during adrenal insufficiency. It was found that the signs of adrenal insufficiency could be made to disappear when such a fluid mixture was substituted for the distilled water used in the control periods. The authors feel, however, that the salt mixture used is not adequate, since some animals while on this mixture died spontaneously of insufficiency after two or three months.

A comparison of results was made between the use of the salt mixture and normal saline as treatment fluid.

The studies presented suggest that the adrenal gland probably regulates, in some way, the metabolism of the salts and the water of the body.

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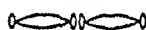
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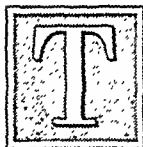
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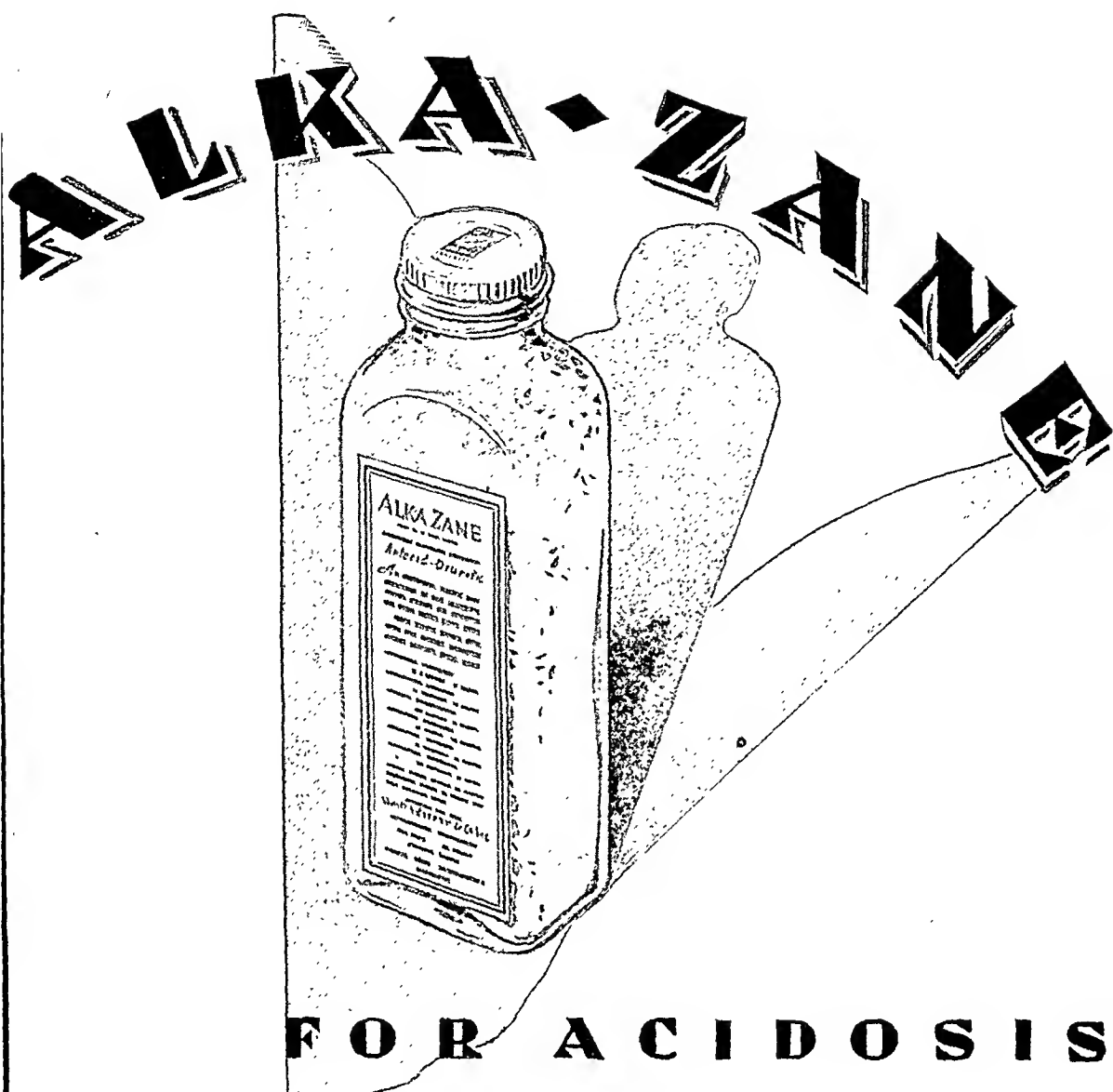
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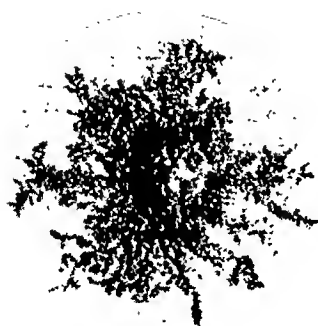
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Professor of Medicine and Director of the Clinic of Medicine and Neurology at the University of Würzburg, Germany

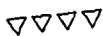
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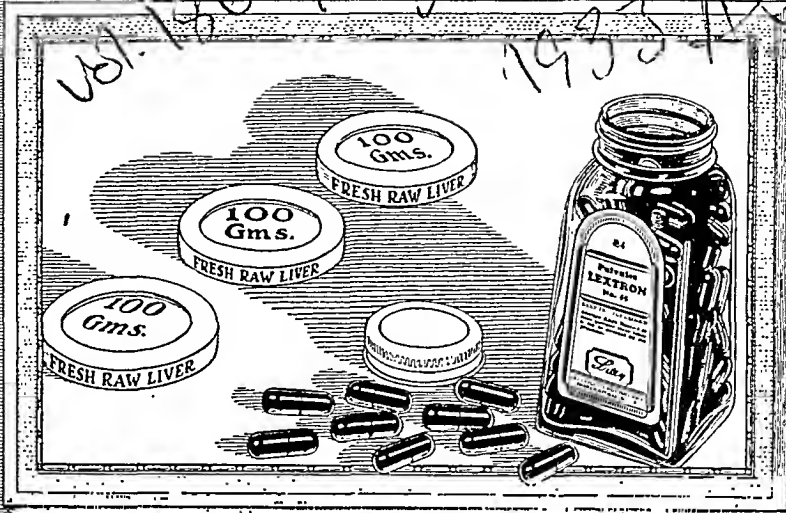
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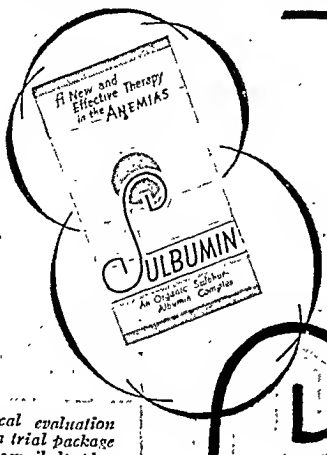
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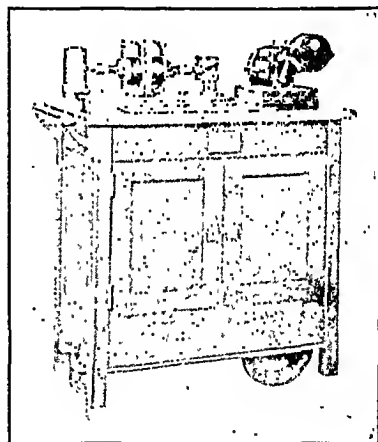
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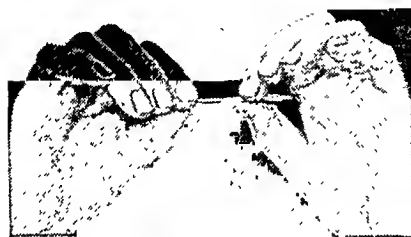
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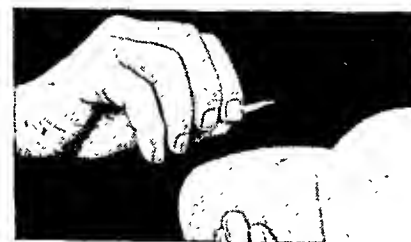
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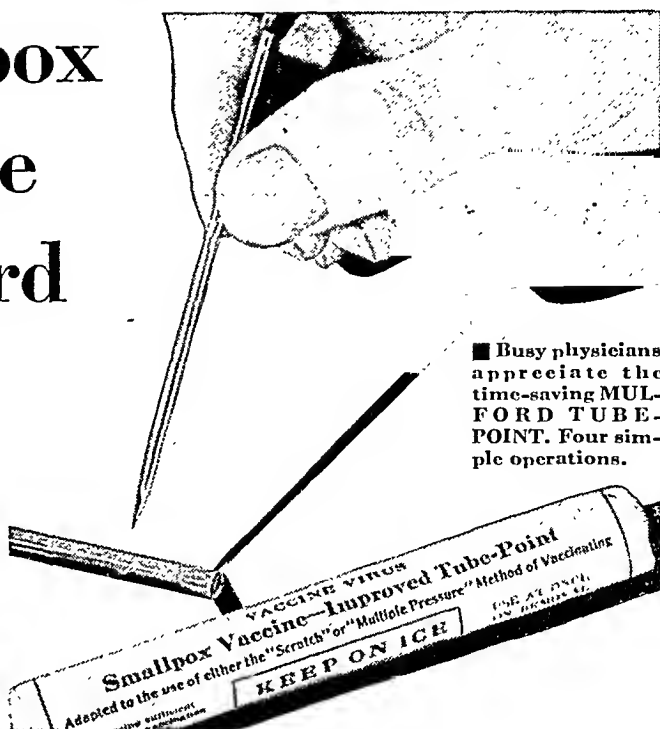
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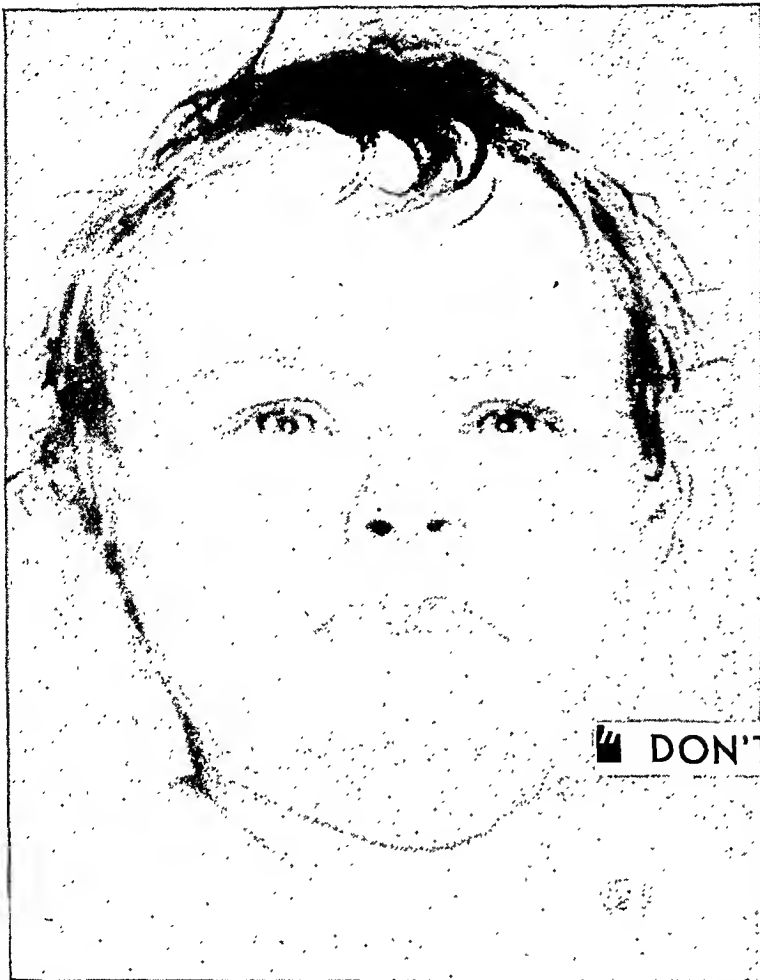
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# Calcium Metabolism and Calcium Therapy

By ABRAHAM CANTAROW, M.D.

Instructor in Medicine, Jefferson Medical College; in Charge of Laboratory of Biochemistry, Jefferson Hospital; Assistant Physician, Philadelphia General Hospital

WITH A FOREWORD BY

HOBART AMORY HARE, B.Sc., M.D., LL.D.

Late Professor of Therapeutics, Materia Medica and Diagnosis in the  
Jefferson Medical College, Philadelphia

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## FROM THE FOREWORD

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HOBART AMORY HARE, B.Sc., M.D., LL.D.

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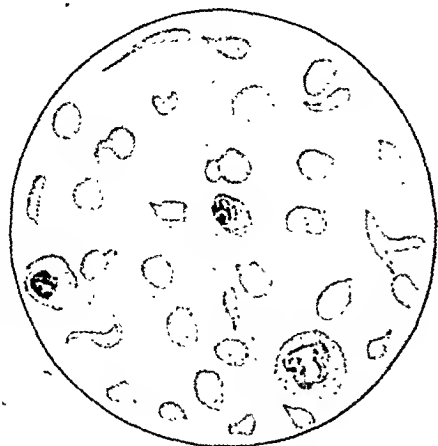
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OF THE MEDICAL SCIENCES

AUGUST, 1933.

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ORIGINAL ARTICLES.

A MODERN PLAN FOR A COMMUNITY CAMPAIGN AGAINST  
AIR POLLUTION.\*

By H. B. MELLER,

HEAD, AIR POLLUTION INVESTIGATION, MELLON INSTITUTE OF INDUSTRIAL RESEARCH,  
PITTSBURGH, PA.

THE invitation which brought me here is regarded by the Mellon Institute of Industrial Research as fresh evidence that medical associations in this country are giving serious consideration to the problem of air pollution, presumably with a view to exercising leadership in the promotion of preventive measures. This attitude on the part of the College of Physicians is quite in line with the accepted traditions of Philadelphia, the home of internationally famous scientific societies. Mellon Institute feels honored at being asked to collaborate with you in planning for consideration of the abatement of smoke in Philadelphia. Medical societies in other cities will watch what is done here.

**Air, Water and Food Purity Equally Important.** Pure air is primarily a medical consideration. Logically, its maintenance is a municipal health department responsibility, just as are pure food and pure water. In the presence of city-wide contamination of his food, his water supply or the air he must breathe, the average citizen is helpless to protect himself or the members of his family. He is compelled to take what the city offers him. When aroused to danger, his instinct and his experience tell him to turn to the physician for protection and guidance. In response to a popular demand

\* Presented at a stated meeting of the Section on Public Health and Industrial Medicine of the College of Physicians of Philadelphia, March 31, 1933.

of this kind, the medical profession was found in the forefront of the movements which gave municipalities pure food and pure water. A parallel movement for pure air fell short of establishing thoroughgoing control. Generally the prevention of dense smoke was about all that was aimed at. Only now is the public coming freely to understand that other and unregulated products of fuel combustion are much more harmful.

In view of the inadequacy and inconclusive character of existing legislation, and also because prompt action may bring unusually desirable economic benefits, the time seems ripe for the medical profession to reassert its leadership and to make hygienically pure air an accomplished fact. A development of this kind in medical circles would be in line with the rapid growth of preventive medicine, which includes air hygiene. The initiative and guidance of physicians are necessary to the success of the cause of air hygiene.

Since 1911 Mellon Institute has been conscious of the relevancy of medicine in formulating its research, and has consistently sustained medical interests in their work to mitigate air pollution. In that year it turned to the Pittsburgh School of Medicine for study of the hygienic aspects of the smoke problem. Oskar Klotz, then professor of pathology, and his associates undertook the study. Their comprehensive printed report of the damage done to health by products of combustion is recognized as a classic; it has been a standard work of reference for two decades.

At that time we recognized that the engineer was interested because of fuel economy and the effects of the products of combustion on constructional material. We recognized that the economist was interested from the viewpoint of waste, added expense in cleaning, loss of natural daylight and such phases of the problem. But after all was said and done, the most influential fact in the effect of air pollutants, particularly products of combustion, was health. This angle controlled the formulation of the Pittsburgh ordinance, which ordinance has served as a model for similar legislation in many cities. When the Bureau of Smoke Regulation was organized it was placed in the Department of Health—a practice that was widely followed over the country.

With the passage of years, Mellon Institute has seen success achieved in reducing the dense smoke nuisance emanating from the regulated portions of its home city, and it has consistently adhered to its policy of insisting on medical and public health participation. Even now the Institute is sustaining Ralph R. Mellon and his staff at West Penn Hospital in a study which has for its aim the more accurate determination of air-borne diseases.

In the light of the character of these developments, I come before you as one fully cognizant of the high importance of the strictly medical and public health aspects of smoke abatement.

It must be recognized that, because the physician is the store-

house of needed medical information, he therefore is the sound guide in air hygiene. He knows that inhaled solid particles irritate the sensitive membranes of the nose, throat and lungs, and may prepare a predisposition to acute diseases of the respiratory tract; that smoke and dirt in the atmosphere reduce the amount of natural sunlight received; that this reduction is proportionately greater in the shorter wave lengths, particularly in the therapeutic band of ultraviolet radiation, the natural source of vitamin D; that bright, sunny days are stimulating, while gloomy, smoky days are depressing; that smoke and dust aid in the formation and prolongation of fogs, with their coincident effects; and that, in other ways as well, bodily wellbeing is affected. The rôle of the physician is fundamental; he is looked to by the public to point out health hazards and to work for their elimination; and he is equipped to set the standard for atmospheric cleanliness—a standard which the engineer will then arrange to meet. The public commitment of the physicians in a community to a campaign for pure air will have as much force as the combined arguments of all other protagonists.

*Smoke Regulation.* With exceptions so few as practically to be negligible, cities that have anti-smoke ordinances regulate only dense smoke. Generally speaking, this means that, unless the density is such that it is impossible to see through the column of smoke as it leaves the stack, there is no violation. And even this opaque smoke is permitted for periods ranging from 1 minute in 8 consecutive minutes to 6 or 8 minutes in 1 hour. Thus it is allowable for a stack to smoke continuously, unless the duration of *opaque* smoke exceeds the time limit. And, of course, solids that do not color the smoke stream, and noxious and obnoxious gases, are not included in the prohibition.

Ordinances prescribe that only such equipment may be installed as can be operated within the limits set, with no provision for reducing those limits as an incentive to manufacturers to produce more advanced designs. After this equipment is installed and in operation, enforcement becomes a matter of observation and supervision on the part of the city inspectors. It is obvious that, under such conditions, results will be in direct proportion to the number of inspectors and their efficiency. Cities have not felt justified in employing large enough inspectional forces for close, continuous control. Consequently, while in many communities it has been possible to maintain a fair degree of compliance, in others enforcement has been little more than a gesture.

The volume of stack dirt is proportional to the amount and smoke-making possibilities of the fuel used. The use of automatic stokers and of semi-smokeless boilers, smokeless fuels in boilers not designed for high volatile coal, better firing methods—all have aided in reducing the amount of visible smoke. The good that might be accomplished has been limited by failure to regulate light smoke

and to exercise control over cinder and ash. Then, too, in all except a few instances, private homes and the smaller apartment houses have been exempt from any regulation as to equipment, fuel or smoke. The necessity for control of domestic smoke-making has been very definitely emphasized during the past three winters. With industrial activity at a low ebb, it has been possible clearly to see the part played by the heating plants in maintaining a smoke nuisance.

The wind is depended upon to carry away the finer solids and to distribute them over wide areas. As the carrying power of the wind is proportional to its velocity, it follows that a low velocity will bring higher concentrations in limited areas, often resulting in formation of a smoke pall or aggravation of one already formed.

Smoke abatement as it has been practised has been instrumental in greatly reducing the amount of visible smoke, in effecting material individual savings in fuel cost, in providing a cleaner atmosphere than formerly with a higher percentage of sunshine, and in reducing cleaning and lighting bills. In other ways as well, smoke abatement has been of tremendous benefit. There is no argument against it; but we still have a smoke nuisance, largely because the extent to which smoke and stack dust can be eliminated has not generally been understood.

Early ordinances necessarily were compromises. A minority protest was smothered by a majority belief that smoke and prosperity were inseparably connected; plant owners feared possible unreasonable restrictions through unintelligent or unsympathetic enforcement; limitation of the amount of smoke to be permitted had to be made in the light of current combustion practice and availability of equipment designed without any such definite restriction; home owners did not take kindly to the idea of regulation, although willing and often eager to have the industrial and commercial plants controlled.

Later ordinances throughout the country generally have been patterned after those earlier compromises. As a result, the advance in smoke abatement has been neither as rapid nor as great as it could have been. The market affords better fuel-burning equipment than ever before; a large percentage of these devices could meet requirements much more strict than those now in force. It would seem wise, from the standpoint of efficiency as well as of cleanliness, to take full advantage of what has been done and to press for additional advances.

Further limiting the effectiveness of smoke abatement is the inability of a city to exercise any control beyond its geographic limits. Manufacturing centers usually are surrounded by smaller industrial communities in which there is little or no regulation of smoke. Wind-borne products of combustion from each such community are carried over and into every other in the group, so that

effort on the part of the central city to clean up is made less decisive by the effects of contaminants originating in parts of the area over which it has no jurisdiction. It is obvious that there should be either unified control or uniform regulation throughout the district.

Another reason for the failure of smoke abatement (as it has been carried on) to meet with the full measure of success that might have been expected is that it has not had the continuous active backing of the community. After an ordinance is passed and a city bureau is charged with the enforcement, most of those who were active in stimulating public opinion and securing enactment of the necessary law regard their civic duty as completed. They, therefore, fold their hands and sit back to watch an inadequately manned enforcement machine operate. Gradually, as the road to cleanliness becomes steeper and more rocky, the machine slows up or even slips backward. There is a demand for a new driver, when the fault lies not with him, nor perhaps with the machine; the road-mending force has quit work. To be permanently successful, smoke abatement like any other constructive program must have the solid support of the people. Passivity is much more difficult to combat than resistance.

*Stricter Regulation.* Considering the fact that equipment is available to satisfy much more stringent requirements than are now being applied with more or less success, it is comparatively easy to indicate the limits to which existing ordinances could be raised or which could be set for new ones.

1. By proper selection from among the large number of makes of boilers, furnaces, automatic feeds and control, and with intelligent care, *dense* smoke could be eliminated in normal operation. The allowance for *light* smoke would vary; in communities where only smokeless fuel is used, restriction could be greater than in sections where high volatile coal is used and where the degree of smokelessness depends upon the equipment and its operation and not on the fuel.

2. Alterations and repairs could be made to conform to such rules and regulations as would insure the same degree of smokelessness.

3. A reasonable time could be allowed for compliance by those whose plants were installed before restrictions were imposed. Serviceable units need not be scrapped, but could be regulated within reason.

4. The use of dust separators would make it possible to eliminate most of the ash nuisance from solid fuels.

5. Ordinances should allow no exemptions—there should be no preferred class. Laws should be framed in such a way that, without the necessity of formal revision by councils, advantage may be taken from time to time of the rapid advances that will be made toward smokeless and dustless use of fuels.

*Campaign for Pure Air.* The familiar type of smoke abatement campaign has features which must be included in any movement toward pure air. It provides for the essential stimulation of public opinion; it affords an opportunity for a considerable amount of valuable general education; it prepares the way for needed legisla-



tion. All of these are necessary, and every community has some public-spirited persons, accustomed to lead in civic matters, who will be found willing to organize and direct that part of the work.

More than this is necessary, however. As a physician first examines his patient, makes his diagnosis, then gives him the necessary treatment; so, in a campaign looking toward pure air, it is requisite to determine the nature and extent of the pollution and to ascertain the sources and causes, when the remedy in the form of regulations can be applied.

Logically, the first step is the organization of an air hygiene district, to include all parts of the smoke area, and the selection of a group to constitute an Air Hygiene Commission. The membership of this group should include representation from the medical, chemical, engineering and architectural professions; the financial, manufacturing, commercial and real estate groups, and the local government.

**Survey of Atmospheric Pollution.** To secure information as to the extent of pollution by products of combustion, actual measurements must be made. Some of these are direct, as the amount and chemical composition of sootfall, and the number and size distribution of air-borne solids; others are indirect, as the effect of air pollution in screening out sunshine, particularly in the ultraviolet region.

**Sootfall.** The collection of solid matter that falls by gravity or is brought down by rain. The smoke area is divided into districts, according to the number of stations deemed necessary to give the desired results. Naturally the greater the number of such stations, the more accurate the information as to conditions in small sections of the area. Proper containers are placed at the stations, to collect solids that fall by gravity or are brought down by rain. These collectors, when changed periodically, are conveyed to the laboratory, where the deposit can be weighed and analyzed for tar, combustible other than tar, ash, etc.

Information then will be available from which to make a dirt chart of the city, so far as sootfall is concerned, to note variations from time to time and, in connection with other data secured in ways that will be mentioned, to make comparisons as to current conditions, including health.

**Air-borne Solids.** There is an intermediate size range of particles that, at a fairly high wind velocity, will be carried in suspension, but at a lower wind velocity will fall. Such particles may be picked up, carried awhile and dropped, and this process repeated many times. These, with particles that are gravitating normally to the earth, and other particles so small as to remain in suspension indefinitely, are the air-borne solids which must be measured.

There are several methods of accomplishing the result. One such will give continuous record of the effect of such particles in

discoloring filter paper; another will collect an average sample over a period of time and permit microscopic study of the solids; still others are designed for instantaneous sampling, followed by determination (microscopically) of the number and size distribution of the particles. In a survey of any magnitude, a combination of these likely would be used. The last-named type has the advantage of ready portability, so that one person may take a number of widely distributed samples in a day.

*Sulphur Dioxid.* The concentration of sulphur dioxid, if desired, may be determined by a standard method.

*Natural Sunshine.* This is a free gift, to utilize which the human organism was developed through the ages. In building up his cities, man has placed a smoke and dirt screen between himself and the sun, so that he no longer receives all of the benefits to which he is entitled from the source of energy. To obtain knowledge of the extent to which this screen exists in smoky sections, compared with a clean suburb, for example, or the country, measurement of natural solar radiation is essential. The survey should include determination of the infrared, the visible and especially the ultraviolet radiation.

Due to the recent development in photoelectric cells, it is possible to secure continuous records of a part of the infrared, of the visible and of the ultraviolet radiation. For the central station and any other control stations that are set up, the records should be continuous. For readings at other stations, or elsewhere, a portable set, with indicators, can readily be devised.

*Other Meteorologic Data.* Temperature, relative humidity, sky conditions, rainfall, wind velocity and direction are recorded by the United States Weather Bureau. This information is available for correlation with the data from the sootfall, air-borne solids and sunshine studies.

Upon this knowledge of the amount and character of deposited and air-borne impurities to which the urban dweller is subjected, and of the amount of solar radiation, particularly in the ultraviolet, of which he is unnecessarily deprived, the physician will be able to base his advice.

This survey of atmospheric pollution is the part of the air hygiene program in which the physician will find most interest; the fact-finding is fundamental, and is necessary to show the magnitude of the nuisance and the extent to which it should be abated.

The scope, details and complexities of a study of atmospheric pollution, as outlined above and in paragraphs which follow, may not be generally understood; its necessity may not be appreciated. But, in the light of known damages and demonstrable benefits, science says the city of the future will collect regularly such information as an integral part of its public health work. Science foresees a city population which will view preventable air pollution with

the same intolerance it now displays toward water and food supply contamination.

**Sources and Causes of Pollution.** A survey, directed by mechanical engineers, should be made to determine the present condition of fuel-burning equipment, with special reference to its classification as: (1) Obsolete or worn out; (2) needing extensive alteration or repair; (3) requiring only minor repairs; (4) indicating change in fuel or firing method only as necessary.

There should be a comparative study, directed by engineering talent, of fuel-burning equipment and fuels offered on the local market, with a view to determining possibilities in efficiency, economy and cleanliness.

Such studies are particularly timely, because of the almost universal undermaintenance during the past 3 years, which has resulted in a country-wide need for replacement of a great deal of fuel-burning equipment and extensive alterations and repairs to much more, to prepare industrial and commercial plants for efficient operation when the present emergency ends. Then there is the vast number of heating plants that need to be replaced or repaired, or in which a different type of fuel should be used. There is an unprecedented amount of work that will have to be done to bring the plants to a condition equivalent to that before the crisis, to say nothing of making any advance toward clean air.

As information concerning conditions and needs is collected and classified, there is the opportunity to put local labor to work on the large volume of minor repairs. Major repairs and alterations can be equitably distributed among responsible local contractors. On new work, because of the information which will have been gathered by the commission, attractive prices and terms undoubtedly can be arranged.

Naturally, this is not the only plan that can be followed. It is given here in brief outline to stress the importance of a comprehensive program, to show how it may be possible to set up such standards of clean air as are feasible, and at the same time to do its part in aiding the unemployment situation and to assist owners to secure advantage of exceptional prices and terms for necessary new equipment.

**Legislation.** At the proper time, and in the light of the information gained in the surveys, the commission will be in position to recommend standards to be met (a) by new equipment, (b) in alterations and repairs and (c) by other boilers and furnaces that are currently serviceable. These standards may be embodied in an ordinance for the air hygiene district.

**Economic Applications.** Large-scale application of this or some similar type of campaign plan for pure air might bring economic results which would tie in with work programs that may be developed by municipal, state or federal governments.

A strong demand for fuel-burning equipment easily could step up the work schedule in a number of boiler and stoker plants where employees are idle or on part time. Even mass production might be attained and make possible the lowering of costs, especially to the domestic purchaser.

More distantly a pure air campaign would spur scientific research, which has lagged in some directions, to the task of developing yet more efficient and additional types of appliances and thus broaden the market. The perfecting and marketing of small-size dust separators would become an important industry. A wide market awaits a small stoker, priced within the reach of the "little" home owner.

Cleaner city air will be of vital assistance in the development of the air conditioning industry in smoky cities, by permitting installation of smaller and less costly systems. Currently filtration devices are made large, at consequent greater cost, to take care of "smog" conditions. Also, in smoky centers of population the filters have to be renewed or cleaned more often than should be necessary.

Real estate owners will realize what the smoke nuisance has cost them in the past, and will see the advantage in including air pollution abatement in any rehabilitation program.

**Summary.** We have tried to show that city dwellers have a right, as a matter of public health, to expect the standard of air purity will be brought up to a parity with that already fixed for water and food; that the rôle of leadership in this movement belongs to the medical profession; that current conditions are unusually favorable for campaign success; that a workable plan of campaign would help immediately to reduce unemployment, spur scientific research, aid infant industries and assist in the restoration of real estate values.

In conclusion, be assured that in connection with whatever action you may take you are free to call upon Mellon Institute of Industrial Research for any assistance it may be able to give, in the light of its 20 years of scientific investigation of the problems of air pollution.

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## THE RADIOLOGIC RECOGNITION OF HEART DISEASE IN PNEUMOCONIOSIS.

By JOHN M. DYSON, M.D.,

PHYSICIAN TO HAZLETON STATE HOSPITAL,  
HAZLETON, PA.

THE object of this communication is the consideration of a roentgenologic sign of cardiac disease. First, it is to be emphasized that the importance of this is not generally understood. Then, as a contribution to cardiac radiology, it will be demonstrated that

this sign may be used to diagnose specifically a pathologic heart condition caused by pneumoconiosis.

The silhouette of a normal heart, in the postero-anterior roentgenogram, presents a depression on the left border between the aortic "knob" above and the prominence of the left ventricle below. When this depressed area is replaced by a marked convexity it indicates prominence of the pulmonic artery and conus arteriosus. This fundamental observation was made by Assmann.<sup>1</sup> Slight prominence of the shadow may be seen in otherwise normal hearts of the hypoplastic type. When it becomes large enough to reach a line drawn from the aortic to the left ventricular prominence, it represents enlargement and serves as a sign of right ventricular hypertrophy. This is in accord with East and Bain,<sup>2</sup> who state that with enlargement of the right ventricle "the shadow of the pulmonary artery becomes more prominent, so that the general concavity of the left border becomes filled." Nichols,<sup>3</sup> in conjunction with pathologists at the Philadelphia General Hospital, has followed cases with similar cardiac silhouettes to the postmortem table, and reports the shadow to represent enlargement and hypertrophy of the pulmonic artery and the adjacent conus.

Surveys of the American literature reveal no mention of this important fact previous to 1932 when Nemet<sup>4</sup> stated that "such a configuration of the left cardiac contour indicates marked enlargement of the part of the right ventricle lying between the apex and the pulmonary orifice (so-called outflow tract)."

Right ventricular hypertrophy may thus be recognized in cases of mitral stenosis or congenital heart disease. According to East and Bain<sup>2</sup> it may be found also in emphysema. Kerley<sup>5</sup> notes (in quoting both Assmann and Schinz) that enlargement of the pulmonary artery may be due to certain acquired diseases which cause stasis in the pulmonary circulation, notably mitral stenosis, Ayerza's disease, and fibroid phthisis. Nemet<sup>4</sup> remarks that the "recognition of right ventricular enlargement is of great significance, and is the only indication of structural change of the heart in the important group of cardiac insufficiency developing in cases of long-standing pulmonary fibrosis."

Practitioners in the anthracite coal regions recognize that cardiac failure is a frequent cause of death in pneumoconiosis. A definite cardiac lesion is generally not diagnosed, however, since there is no enlargement of the transverse diameter of the heart. It is my purpose to point out that pneumoconiosis, a disease of long-standing pulmonary fibrosis, causes obliteration of much of the vascular bed in the lungs. It is reasonable to suppose that the first chamber of the heart to show reactionary change is the right ventricle. The proposition is made, therefore, that the convex shadow of the left border described above (when observed in miners with no other indication of heart disease) be regarded as evidence of right ventric-

ular hypertrophy caused by pneumoconiosis. The following cases exemplify the proposition.

**Case Abstracts.** CASE 1.—J. K., a white male, aged 49 years, was admitted to the White Haven Sanatorium with a provisional diagnosis of tuberculosis complicating pneumoconiosis. He complained not only of cough and expectoration but also of swelling of the ankles. He had been a miner for 27 years and had used the jack-hammer for 5 years. Observations made by Dr. Ross K. Childerhose of the sanatorium staff at that time (1931) included: "Temperature was always normal. He was 12 per cent underweight, and had slight cardiac decompensation. There was moderate cough with 3 fluidounces of expectoration daily. Eighteen sputum examinations were negative for tubercle bacilli as well as two 24-hour collections for concentration and culture methods." In August, 1932, he was brought to the Hazleton State Hospital for study. There was no history of rheumatism or syphilis. Physical examination was negative except for moderate emaciation and a fairly loud to and fro murmur over the pulmonic area. Blood Kahn test was negative. A roentgenogram made at this time was no different from that made at White Haven which disclosed pneumoconiosis, shadows suspicious of tuberculosis, and enlargement of the pulmonary artery and conus shadow. Electrocardiographic examination showed right axis deviation (Fig. 1).

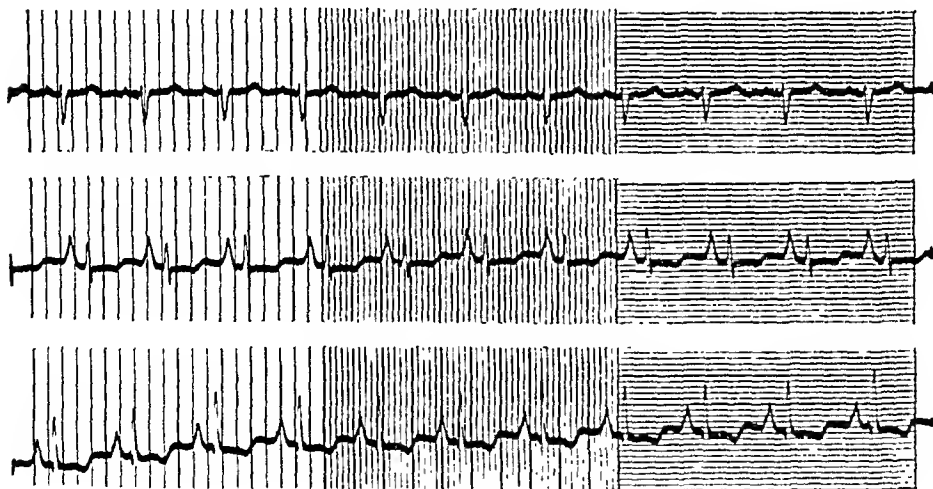


FIG. 1.

*Comment.* The roentgenogram (Fig. 2) shows no enlargement of the transverse diameter of the heart. The sign of right ventricular hypertrophy can be demonstrated quite definitely, however.

CASE 2.—A. G., a frail white man, aged 51 years, a miner for more than 30 years, admitted to the medical service on September 21, 1931, presented weakness of the arms and legs, in addition to cough, expectoration and substernal pain. Physical examination showed a rapid but regular heart action. Cardiac sounds were "distant and diminished in intensity." Fine râles were heard in each base. Moderately advanced arteriosclerosis was present. No other observations were remarkable except the neurologic examination which disclosed progressive spinal muscular atrophy. Laboratory findings, including blood and spinal fluid Kahn tests, were normal.

## DYSON: HEART DISEASE IN PNEUMOCONIOSIS

Roentgenologic examination showed third stage pneumoconiosis and a very prominent pulmonary artery and conus shadow. This man left the hospital against advice 4 days later, and died at home in April, 1932. No electrocardiogram was obtained.

*Comment.* The roentgenogram (Fig. 3) confirmed the clinical impression of heart disease.

CASE 3.—M. F., a white male, aged 52 years, came to this hospital in September, 1932, with symptoms of cough, dyspnea, and swelling of the ankles, worse in the last 2 weeks. He had worked in the mines for 10 years, and had handled the jack-hammer for more than 1 year. There had been no rheumatic symptoms, no tonsillitis, and no venereal infections in his past history; his wife had had 6 children (5 living and well) and no miscarriages. There were no other noteworthy facts in his history. Physical examination revealed dyspnea, slight enlargement of the area of cardiac dullness to the right, exaggeration of the pulmonic second sound, râles in each base, and edema of the ankles. Blood Kahn test was negative. Roentgenologic chest examination reported third stage pneumoconiosis and hypertrophy of the right ventricle of the heart. Right axis deviation was found on the electrocardiogram (similar to Fig. 1 and Fig. 6). This man, slightly relieved by hospitalization, returned to his home and is still living.

*Comment.* Right-sided hypertrophy here (Fig. 4) has not only "filled out" the left border of the cardiac silhouette but has caused enlargement of the transverse diameter to the right.

CASE 4.—J. G., aged 45 years, was a miner for 26 years, using the jack-hammer for the last 7 years. Because of cough, weakness and blood streaked sputum he had been admitted to the White Haven Sanatorium for a month in August, 1932. There was no fever during that time. Moist crackling râles were found in the lower half of each lung, as well as extensive consolidation in the upper halves. Eleven sputum examinations were negative for tubercle bacilli. In October, 1932, he came to the Hazleton State Hospital because of distressing cough, expectoration and anorexia. Nothing in his past life suggested syphilis or rheumatic fever. Prominent findings included emaciation, copious thin expectoration, marked decrease of respiratory excursions, loud moist râles throughout the chest, and an accentuated pulmonic second sound. Urinalyses and blood counts were not abnormal, and the Kahn test proved negative. Roentgenologic studies showed third stage pneumoconiosis and a cardiac shadow suggestive of pulmonary artery enlargement. Electrocardiography produced a tracing of right axis deviation (similar to Fig. 6). After 2 weeks' hospitalization during which he received insulin and the high caloric régime advocated for emaciation, this patient gained 6 pounds and improved enough to be discharged to the dispensary.

*Comment.* Fluoroscopy demonstrated the pulmonary artery prominence more conclusively than the roentgenogram (Fig. 5). The reactionary enlargement of this structure here might be caused by the drag of adhesions as well as decrease in the pulmonary vascular bed. This would be in agreement with Dietlen,<sup>6</sup> who cites as a case in point chronic pulmonary tuberculosis with fibrotic lung tissue dragging on the pulmonary artery. Kerley,<sup>5</sup> and Pancoast and Pendergrass<sup>7</sup> also admit of this possibility.

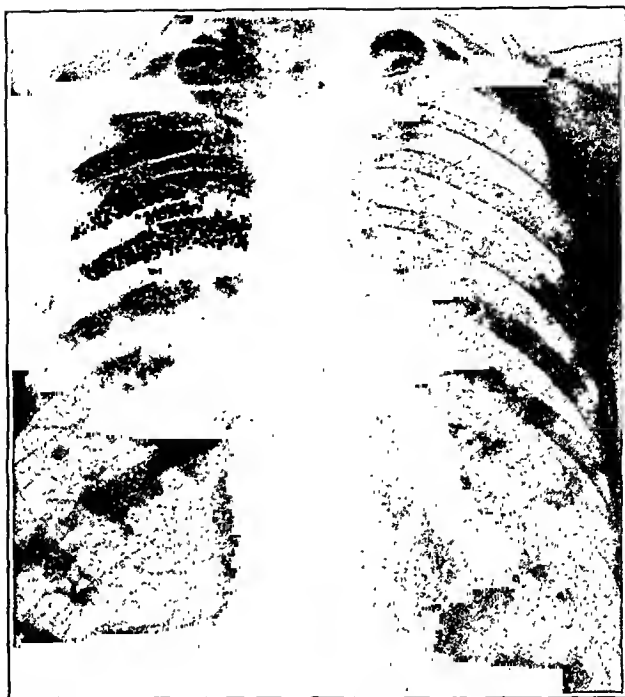


FIG. 2.—Case 1. Roentgenogram shows difficulty of excluding tuberculosis. Left cardiac border presents prominent shadow of the pulmonary artery and conus.



FIG. 3.—Case 2. Roentgenogram taken September 22, 1931. In addition to the pneumoconiosis the shadow on the left border of the heart is clearly seen.



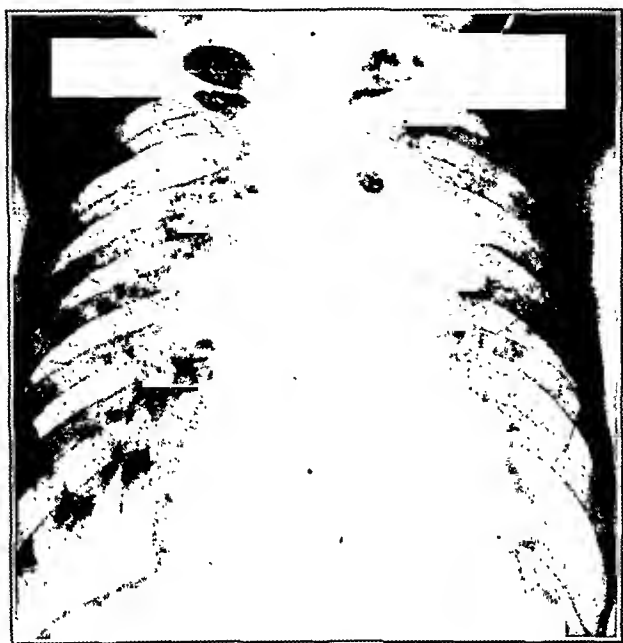


FIG. 4.—Case 3. The left cardiac border is filled out. Right ventricular hypertrophy.



FIG. 5.—Case 4. No enlargement of the transverse diameter of the heart. Pulmonary artery and conus prominence indicate reaction of the right heart to the marked pneumoconiosis.

CASE 5.—H. C., a white male, aged 43 years, was referred to this hospital in October, 1932, for gastro-intestinal studies. His presenting symptoms of diarrhea and lower abdominal discomfort were of only 2 weeks' duration. He had suffered, however, with cough, dyspnea and some dysphagia for 6 months. These were becoming worse instead of better. For 17 years he had worked in the mines, and for 6 months had used rock drills and jack-hammers. He had never had rheumatism, tonsillitis or syphilis. Three children are living and well and his wife had had no miscarriages. Physical examination disclosed nothing remarkable other than limited respiratory excursions, evidence of fibrosis in the upper lobes, and loud, coarse râles throughout the bases. Laboratory studies including the Kahn test were negative. Roentgenologic study of the chest showed third stage pneumoconiosis, most marked in the upper halves of each chest, and a cardiac silhouette indicative of pulmonary artery and conus prominenece. An electrocardiogram was made which showed no abnormalities except right axis deviation. After these examinations were completed the patient returned home. No organic disease of the stomach or intestines could be demonstrated.

*Comment.* The roentgenogram is similar to Fig. 5. The electrocardiogram (Fig. 6) shows the same feature observed in Cases 2, 3 and 4: inversion of the main deflection of the *Q-R-S* complex in Lead 1.

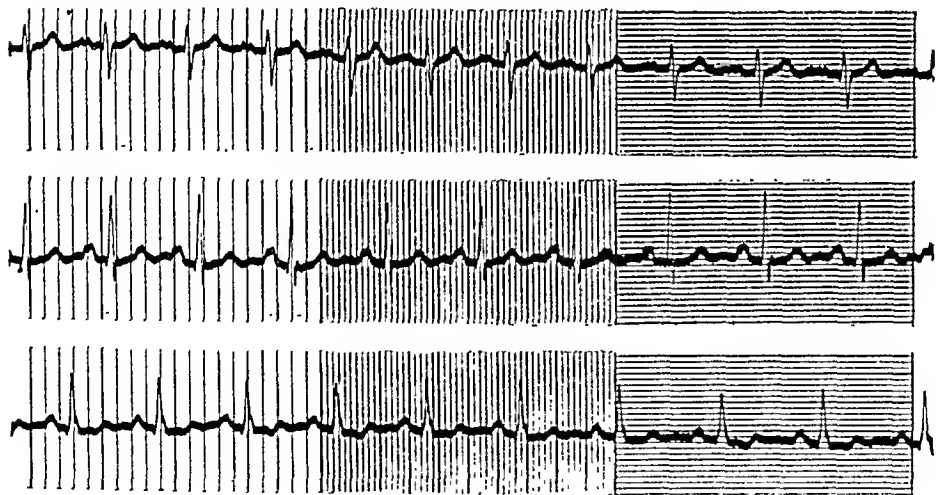


FIG. 6.

**Summary and Conclusions.** 1. The roentgenologic sign of hypertrophy of the pulmonary artery and the right ventricle is described, and its importance emphasized.

2. Five cases, with their roentgenograms, are presented to demonstrate how this sign may be utilized to diagnose right ventricular hypertrophy due to pneumoconiosis. Electrocardiograms were made in 4 of these cases, each of which presented right axis deviation.

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**THE HEALING OF TUBERCULOUS CAVITIES:  
A CLINICAL STUDY.\***

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THE prognostic significance of an open cavity in a tuberculous patient, particularly at the time of discharge from a sanatorium, is generally recognized. In 1916 King<sup>1</sup> showed that patients discharged from Loomis Sanatorium with sputum which had changed from bacillary to non-bacillary had a mortality at the end of 5 years of 225 per 1000, as compared to 710 per 1000 of those in whose sputum tubercle bacilli were demonstrable at time of discharge. Obviously the curability of tuberculous cavities is of first importance, and yet the literature on the subject is replete with conflicting views. According to Gräff,<sup>2</sup> the presence of cavity portends the death sentence for the patient. He modifies this remark by stating that this sentence frequently is not carried out for several years. Barnes and Barnes,<sup>3</sup> in a study of 1454 tuberculosis cases with cavity found a mortality of 80 per cent within 1 year. In contrast with this figure Fales and Beaudet,<sup>4</sup> in 120 cases with cavity, reported 48 (40 per cent) healed spontaneously. These cases represented 147 cavities, 62 (42 per cent) of which healed. Fischel<sup>5</sup> found that, in those cases receiving institutional care but no other form of treatment, results were so disappointing that he concluded that the existence of pulmonary cavity in poor patients calls for a more

\* Paper read before the American Sanatorium Association (Eastern Section) at Waltham, Mass., October 14, 1932.

active therapy, the aim of which should be the obliteration of cavities before the patient is discharged.

In order to reconcile these conflicting and extreme views, and to determine, if possible, significant prognostic factors as to the curability of cavity, a detailed study was made of 296 cases with tuberculous pulmonary cavities at Loomis Sanatorium.

**Plan and Scope of Study.** Only those cases were included in this study that had cavity demonstrable roentgenographically and tubercle bacilli in the sputum. The minimum period of our observation was 3 months, the shortest period considered to be sufficient to establish at least a trend in the course of the disease. There were but few, however, in this minimum observation group, the average period of observation of the whole group being about 13 months. Cases were taken consecutively from the files of Loomis Sanatorium over a period of 3 years (1928 to 1931); of the 800 cases examined only 296 fulfilled the criteria for inclusion. The following factors were recorded in each case: age, sex, period of observation, side of lesion, size and location of cavity as observed on stereoscopic P. A. Roentgen rays, type of cavity wall and nature of surrounding infiltration; estimate from the history of the duration of the disease and cavity; the amount and bacillary content of the sputum; constitutional reaction (temperature, pulse rate, toxemia); complications; status of body weight as compared with standard; diagnosability of cavity from physical signs and changes in physical signs; duration of bed rest and exercise. Notation was made of the significant changes in the serial Roentgen rays and all the above factors correlated for that particular time. The induction of collapse therapy was indicated and progress thereafter reported.

Since it is of primary importance to determine what actually can be expected in the way of spontaneous healing of cavities, the 296 cases were first classified according to the criteria listed below. If they received no collapse therapy this classification was final. If they received collapse therapy they were classified first on the basis of the changes that had occurred spontaneously and then again to show the results of collapse therapy. In order to avoid confusion in cases receiving collapse therapy soon after admission, an arbitrary time limit of 2 months was set, and all cases receiving collapse therapy within this short period were classified in a separate group, the *Early Collapse Therapy* group, according to the result of this therapy. Thus we have an initial classification arrived at on the basis of spontaneous healing, plus the "early collapse therapy" group, and final classification after adding in the results of later collapse therapy.

The criteria for the initial, and for our purpose most important, classification were as follows: 1, *Spontaneous closure*—sputum negative on concentration for at least 3 months; the shadows representing cavity to be no longer present on the Roentgen ray. 2, *Much*

improved—marked shrinkage in size of cavity, which should not exceed 1 by 1 cm.; sputum negative or positive. 3, *Slightly improved*—total cavity reduced in size, but in excess of 1 by 1 cm. 4, *Unimproved*—Roentgen ray and pathologic anatomy substantially unchanged or worse, irrespective of clinical improvement. Clinical improvement as evidenced by gain in weight, reduction or disappearance of fever was recorded, but did not influence the final classification. Thus, according to the American Sanatorium Association, a patient might be classified as *quiescent*, but in our study would be *unimproved* because of the essentially unchanged pathologic anatomy.

TABLE 1.—RESULTS OF TREATMENT BY BED REST ALONE AND AFTER COLLAPSE PROCEDURES.

	Results of treatment by bed rest alone (spontaneous healing).	Received collapse therapy after observation.	Results of collapse therapy.		Final results, combining spontaneous healing with collapse therapy.
			Cavity closure secured.	Other changes in status.	
Cavity closure secured . . .	65* = 22%	....	....	.....	115 = 38.8%
Much improved . . . . .	38 = 13%	3 { 1 P 2 Ph	2 { 1 P 1 Ph	1 remained much improved	72 = 24.3%
Slightly improved . . . .	47 = 15%	23 { 8 P 12 Ph 1 P+Ph 2 Th	3 { 1 P 5 Ph 2 Th	6 became much improved 9 remained slightly improved	53 = 17.9%
Unimproved . . . . .	84 = 28%	57 { 39 P 17 Ph 1 Ph+Th	13 { 10 P 3 Ph	18 became much improved 9 became slightly improved 17 remained unimproved	56 = 18.9%
Given early collapse therapy (No preliminary observation)	62 = 21% 54 P 8 Ph		27 { 20 P 3 Ph 1 Ph+P 3 P+Th	12 became much improved 11 became slightly improved 12 were unimproved	

\* All figures refer to cases, not individual cavities.

P = received therapeutic pneumothorax; Ph = received phrenicectomy; Th = received thoracoplasty.

Application of these criteria for classification gives us the figures of Table 1. The 296 cases, classified according to the Sanatorium Association classification, were divided into 36 per cent "moderately advanced" and 64 per cent "far advanced." The number and percentage of the 5 major groups are shown first. There were 65 cases (22 per cent) in the spontaneous closure group. To make the study complete the subsequent course of the other groups and the influence of collapse therapy on their final status, is indicated. The question may be raised: Why did not more (only 3 of 38) of the "much improved" group later receive collapse therapy, in contrast with the "slightly improved" and "unimproved" groups, of whom 50 and 60 per cent respectively, received collapse therapy?

The reason is that these patients were too well for such therapy and from their past favorable progress it was reasonable to anticipate spontaneous closure. Of the 23 first classified as "slightly improved" and then receiving collapse therapy, 33 per cent obtained closure. Of the 57 first classified as unimproved prior to collapse therapy, 22 per cent obtained closure. Of all who received collapse therapy in these groups 24 per cent obtained closure. Of the 63 in the "early collapse" group, 37 per cent obtained closure and an additional 6 per cent by supplementary surgical procedures. Summing up the results obtained in the whole group shows 65 (22 per cent) obtaining closure spontaneously and 50 (17 per cent) obtaining closure as the result of different forms of collapse therapy. Thus a total of 115 (39 per cent) of the 296 cases eventually were classified as arrested disease.

The markedly higher percentage of closure recorded for the early pneumothorax group (37 against 24) immediately attracts attention and demands explanation. The answer, after analyzing the cases in the two groups, appears to be that it is rather the type of case than the early collapse that gives a higher percentage of closure in the early collapse group. Of 54 early pneumothorax cases, only 4 (7 per cent) had excavation in the contralateral lung, while in the later group of 50 cases, 26 (52 per cent) had cavity in the so-called "good lung." In many instances in the latter group, pneumothorax was withheld until healing changes were demonstrated in the contralateral lung. In others pneumothorax was given in spite of obviously unhealed or unhealing cavities in the hope of obtaining benefit from control of the main focus of disease. In several cases bilateral pneumothorax was given.

**Analyses of Factors Influencing Healing.** *Side of Cavity.* The frequency of right to left to bilateral cases was 42 to 27 to 31. In this series the incidence of cases with cavity only on the right was definitely preponderant. Furthermore, in considering the 65 cases which satisfied the criteria for spontaneous closure, the incidence of healing was greater on the right—more than twice that of left-sided and three times that of bilateral cases. While this series is too small to draw conclusions from these figures, it is felt that at least a trend is indicated in favor of the right side.

*Sex.* In the group studied there were 170 men and 126 women. Practically the same percentage of both sexes appeared in the spontaneous closure group and in the unimproved group. It is felt, therefore, that in any large group the factor of sex plays very little part.

*Age.* In considering age and sex together, however, particularly in different age groups, significant deviations from the average are noted in the percentage of spontaneous closure and of unimproved. The per cent of spontaneous closure for the whole group was 22. Under 25 years, the percentage chance of spontaneous closure was

17. Under 20 the percentage chance of closure for girls was even more significantly less, namely, 11 per cent. Furthermore, the percentage of unimproved was highest in girls under 20 (64 per cent *versus* 28 per cent average). Significant deviation from average in unimproved was also noted in the age group over 45, where a percentage of 40 (*versus* 28 average) was recorded. In other words, resistance to tuberculosis appears to be lower in middle age and adolescence, particularly in young girls.

*Average Period of Observation.* The spontaneous closure group had the shortest average stay (10.6 months). This figure showed increase in the other groups up to 15.9 months as a maximum in the unimproved group. In other words, in terms of the average, the closure group did well fairly quickly, and length of stay in the other groups was longer in proportion to severity of disease and poor resisting powers. The figure for the early collapse group (11.6 months) is comparatively low, and may be explained by the fact that a number of this group returned home after getting a stable pneumothorax, and obtained refills there. As closely as could be estimated, the average length of time for spontaneous closure by our criteria was 5.6 months. This figure is of interest in comparison with the average time for closure in successful pneumothorax cases (5 to 6 months) as reported by Herben and Franklin\* in a study of therapeutic pneumothorax at Loomis Sanatorium.

*The Age of Cavity.* This cannot be estimated accurately from the history. In this study cavity was considered present from the date of the first hemoptysis or first bacillary sputum or appearance of suggestive cough and expectoration. Using these criteria, the average age of cavity for the closure and unimproved groups was, respectively, 5.4 months and 11.1 months, figures roughly proportional to the number of heavy-walled cavities in these groups.

*Body Weight.* Increase in body weight is usually a favorable sign, but not always so. As a general rule, patients and the laity place more emphasis on it than on any other single symptom. The status on admission of the 296 cases was: 39 (13.1 per cent) above standard, 249 (84.1 per cent) below and 8 (2.7 per cent) standard weight. At the end of the period of observation, 227 (76.6 per cent) had gained weight, 62 (20.9 per cent) lost and 7 (2.3 per cent) remained stationary. Analysis of changes in body weight in groups according to final status showed, in the closure group of 65 cases, 56 (86.1 per cent) gained weight, 6 (9.2 per cent) lost and 3 (4.6 per cent) remained unchanged. In the unimproved group of 83, 51 (61.4 per cent) gained, 31 (37.3 per cent) lost and 1 (1.2 per cent) remained unchanged. Estimating progress from gain in weight alone the factor of error is considerable, *viz.*, 61.4 per cent in the unimproved group and 20.9 per cent in the closure group. An interesting finding was that the greatest percentage of cases above

\* To be published.

standard on admission was in the group finally classified as unimproved. This shows that being overweight at start of treatment is not an index of subsequent progress.

*Toxemia.* As indicated in the introduction, temperature reaction was recorded on admission and subsequently in each case. The percentage of cases febrile on admission in the various groups of our classification was: spontaneous closure, 18 per cent; much improved, 23 per cent; slightly improved, 48 per cent; unimproved, 52 per cent; early collapse, 85 per cent. There was a striking parallel between these figures and the percentage of cases with heavy infiltration in the various groups. The high incidence of fever in the early collapse group was one of the chief reasons why a preliminary period of observation was eliminated in that group.

*Complications.* Tuberculous complications had an increasing incidence as the final status was more unfavorable, ranging from 6 per cent for the spontaneous closure group to 30 per cent for the unimproved group. There was no such correlation in the incidence of nontuberculous complications. Twenty-one per cent of the 296 cases had tuberculous and 5 per cent nontuberculous complications.

*Treatment.* In recording the kind of treatment received, it was of interest to note that the average duration of bed rest paralleled the severity of the disease (3.6 months in the closure group to 10.1 in the unimproved group). The influence of prolonged bed rest in securing healing could not be accurately determined because there are no controls. In individual cases, as the study was made, significant episodes were observed which tended strongly to strengthen our impression of the importance of adequate initial bed rest. The average duration of bed rest for the early collapse group (7 months) was about twice that of the spontaneous closure group.

*Sputum.* The fluctuations in the amount and bacillary content of the sputum were found important in individual cases, but were factors difficult to generalize. They are usually proportional to the severity of the disease, but not infrequently there may be little secretion from a large cavity or the patient may be swallowing the sputum, while associated with a small cavity there may be considerable expectoration, either because the patient is sputum conscious, or because there is a secondary complication, as chronic sinusitis. Average figures for 2 by 2 cm. cavities in the closure and unimproved groups were: 10 gm. of Gaffky III (average 1 bacillus in each microscopic field) and 15 gm. of Gaffky IV (average 2 to 3 bacilli in each field), respectively. For 4 by 4 cm. cavities, corresponding figures were: 10 gm. of Gaffky IV and 16 gm. of Gaffky IV. It is observed that the average figure gives very little information, even in the order of a trend.

*Factors Revealed by Roentgen Ray.* Finally, and probably most important, are factors revealed by the Roentgen ray. Of the whole group there were 24 per cent who during observation had Roentgen



ray evidence of extension of their disease. (This figure does not take into account increase in size of cavities already present, but represents new disease.) The spread was commonest on the same side, then both sides, then the opposite side. The percentage of spread of the early collapse group was 25, practically identical with the group as a whole, and here the order of frequency was opposite side, same side, both sides. The incidence shows an increase from 13 per cent for 2 by 2 cm. cavities to 29 per cent for cavities over 4 by 4 cm.

*Extent of Excavation.* Table 2 shows an analysis of the 296 cases according to total diameter of cavities as revealed by the Roentgen ray. Prognostic information of value is immediately apparent. Where the extent of excavation was not over 2 by 2 cm., 48 per cent of the cases healed spontaneously. With excavation totalling not over 3 by 3 cm., this figure dropped to 21 per cent for the group, while in the other two groups (4 by 4 and over 4 by 4 cm.) the figures were 15 and 7 per cent, respectively. Furthermore, the percentage of unimproved showed increase with the extent of excavation. There was little difference in the 2 by 2 and 3 by 3 cm. groups (20 per cent), but thereafter the figure jumped to 35 per cent. Early collapse therapy was infrequent in cavities up to 2 by 2 cm. (9 per cent), but was indicated two and three times as often in subsequent groups.

TABLE 2.—RESULTS ACCORDING TO EXTENT OF EXCAVATION.

Total diameter of cavities.	Spontaneous closure.		Much improved.		Slightly improved.		Unimproved.		Early collapse therapy.		Totals.
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	
2 by 2 cm. . .	34	48	7	10	9	13	14	20	6	9	70
3 by 3 cm. . .	13	21	11	19	13	20	11	19	12	20	60
4 by 4 cm. . .	10	15	8	12	9	14	22	34	15	23	64
Over 4 by 4 cm.	8	7	12	11	16	15	37	36	29	28	102
Totals . .	65	..	38	..	47	..	84	..	62	..	296

Table 3 shows the results of a study of the total 464 cavities from the point of view of size, location, heaviness of surrounding infiltration and type of cavity wall. It should be pointed out that further subdivision into pathologic types is not indicated. While undoubtedly it is important in any individual case to decide whether we are dealing fundamentally with caseous or fibrous disease, for statistical purposes it seems sufficient to record our findings in the terms indicated in the table.

TABLE 3.—FACTORS INFLUENCING HEALING.

Size of cavity.		Size.	Location.			Surrounding infiltration.			Cavity wall.			
			Peripheral.	Central.	Medial.	Slight.	Moderate.	Heavy.	Thin.	Moderate.	Thick.	Honeycombed.
2 by 2 cm.	Number of cavities .	81	38	34	9	3	41	37	19	11	7	44
	Per cent spont. closure	40	31	52	22	66	51	25	52	36	28	37
3 by 3 cm.	Number of cavities .	78	37	39	2	6	36	36	23	12	2	41
	Per cent spont. closure	20	21	25	0	33	19	17	26	17	0	19
4 by 4 cm.	Number of cavities .	97	55	35	7	2	45	43	40	16	4	37
	Per cent spont. closure	13	16	17	15	22	19	9	20	12	0	8
Over 4 by 4 cm.	Number of cavities .	208	122	77	9	12	56	140	72	30	26	70
	Per cent spont. closure	6	4	6	10	16	14	3	8	3	0	5
	Number of cavities .	464	252	185	27	30	178	256	154	69	39	202
	Per cent spont. closure	17	12	22	15	27	22	9	20	13	5	14

The factors named above are doubtless subject to variation with individual interpretation, but since they were recorded uniformly they may be considered suitable for study. The location of cavity, recorded as peripheral, central or medial, upper, middle, or lower third, was determined by stereoscopic Roentgen rays, by fluoroscopy, or by both methods. Surrounding infiltration was denoted as slight, moderate or heavy. The cavity wall was described as thin, moderately thick, thick or honeycombed. The size of honeycombed cavities was estimated according to the extent of the diseased area involved.

Size of cavity is again shown to be important in healing prognosis. Other things being equal, the location of cavity in the lung definitely influences the chances for spontaneous healing. In cavities of all sizes central location was more favorable than peripheral. A medial location is least frequent, but is seen to be more favorable than peripheral in our series.

The nature of the infiltration surrounding a cavity is an extremely important factor in influencing healing. The table shows clearly that the incidence of healing with slight surrounding infiltration is high, while with heavy infiltration it is very low, and the patient is likely to be in the unimproved group. The incidence with moderate surrounding infiltration is higher than midway between the two extremes.

Furthermore, as has been frequently recognized, the type of cavity wall has prognostic significance. It is demonstrated in Table 3 that cavities described as having a thin wall have the best chance for spontaneous healing, while those with a moderate wall have 35 per cent less chance. Cavities with definitely thick wall

do very poorly, and in such cavities over 2 by 2 cm. spontaneous healing was not recorded. Honeycombed cavities occupy an intermediate position, but in general their prognosis was below the average for the group. It is difficult to determine closure satisfactorily in this type of cavity, which may possibly be due to emphysematous blebs, will still be present on the Roentgen ray after the sputum is negative on concentration.

**Comment.** From the above findings the necessity for individualization in the treatment of pulmonary tuberculosis with cavity is demonstrated. The presence of cavity undoubtedly constitutes a serious menace, but before instituting collapse therapy all factors should be carefully weighed; and if they are not highly unfavorable, a preliminary period of observation with the patient at bed rest is fully justified. The danger of spread of the disease during such a period has, except in acute cases, been overemphasized. In this study, of those who had extension of their disease 85 per cent were febrile at the time of spread. From this it may be inferred that, if the patient is afebrile and doing well clinically at bed rest, there is not much danger of spread. Furthermore, collapse therapy does not eliminate this danger, as is shown by the fact that the early collapse group had a 25 per cent incidence of spread after collapse, as compared with 24 per cent for the group as a whole, which contained many hopeless cases. If it is apparent that spontaneous healing is taking place, the bed rest program should be continued with fluoroscopic examination at intervals of not longer than 2 weeks and Roentgen rays at intervals of not longer than 1 to 2 months. If these observations do not reveal satisfactory progress, collapse therapy is indicated. As to the likelihood of the development of obstructive and troublesome adhesions between the layers of the pleura during the preliminary period, there is no positive evidence that such is the case. It is rather the type and distribution of the lesion with involvement of the pleura and not necessarily the duration of the disease which determines whether adhesions will be present. Packard<sup>6</sup> has shown that a good collapse by pneumothorax may at times be brought about in cases of long standing with extensive retraction. At Loomis, several instances have been observed in which there developed, apparently simultaneously with acute extension, surface adhesions directly over and limited to the newly involved area. Without denying the value of collapse therapy there are a number of reasons why spontaneous healing, when it can be obtained, is the most desirable form of healing. First, there is the time element. In this series the average time for spontaneous closure was 5 to 6 months. According to Herben and Franklin, the average time for closure by pneumothorax in cases where this desirable result was brought about was 5 to 6 months; and it must be remembered that this is merely the starting

point, for the lung must usually be kept down at least 2 years and then reexpanded. Furthermore, the average duration of sanatorium residence for the early collapse group was  $11\frac{1}{2}$  months, compared with  $10\frac{1}{2}$  months for the spontaneous closure group, and the average period of bed rest for these groups was 7 months and  $3\frac{1}{2}$  months, respectively. In addition, collapse therapy is not without its risks. In prescribing pneumothorax, the fact is frequently overlooked that complications are the rule rather than the exception. Tuberculous pleuritis complicating therapeutic pneumothorax is very frequent; this is at times so severe as to cause, by reason of pleural thickening and ingrowth of fibrous tissue from the pleura, permanent loss of function of the lung, and necessitate thoracoplasty. In the average pneumothorax case the damage to the lung is out of proportion to the extent of the disease, and marked retraction on reexpansion is frequent. That these objections, however, did not, in our estimation, constitute contraindications, especially when the disease failed to heal or was progressive, is shown by the fact that 49 per cent of the 296 cases received some form or combination of forms of collapse therapy during residence.

**Summary.** A study of 296 cases of pulmonary tuberculosis with cavity (464 cavities) at Loomis Sanatorium showed the following: Classified as to extent of excavation, there were 23.6 per cent with cavity, 2 by 2 cm.; 20.1 per cent, 3 by 3 cm.; 21.6 per cent, 4 by 4 cm., and 34.4 per cent over 4 by 4 cm. Of the whole group 22 per cent secured spontaneous closure of cavity. The chance for spontaneous healing was inversely proportional to the size of the cavity. Closure occurred in 40 per cent of 2 by 2 cm. cavities, 20 per cent of 3 by 3, 13 per cent of 4 by 4, and 6 per cent of over 4 by 4.

Where the infiltration surrounding the cavity was slight, the percentage of spontaneous closure was higher for cavities of all sizes. The heavier the surrounding infiltration the less the chance for closure to a minimum of less than half the average for cavities with heavy surrounding infiltration. Similar relations pertain in considering the thickness of the cavity wall: thin-walled cavities of all sizes, especially with slight surrounding infiltration, do better than the average. The thicker the wall the poorer the chance for healing to a minimum of 5 per cent for thick-walled cavities.

Central location gives twice as good a healing prognosis as peripheral, that is, close to the parietal pleura. Right-sided cavities in this series had twice the percentage of spontaneous closure of left-sided and three times that of bilateral cavities.

The age group 15 to 25 did only about 50 to 75 per cent as well as the average in spontaneous healing, and had a large number unimproved (45 per cent *versus* 25 per cent average). In girls aged under 20 years only about half (11 per cent) the average secured spontaneous closure and the per cent unimproved was 64. Over 45 years there was a high percentage unimproved (40 per cent).

Gain in body weight is shown to be an unreliable index of healing, since 60 per cent of the unimproved gained weight.

The incidence of spread for the whole group, which included many hopeless cases, was 24 per cent. In the early collapse therapy group, the incidence of spread was the same.

Classification made on the basis of spontaneous healing (except for 22 per cent in the early collapse therapy group) showed 22 per cent spontaneous closure, 13 per cent much improved (cavity reduced to a remnant; sputum positive or negative), 15 per cent slightly improved, and 28 per cent unimproved.

Sixty-five per cent of the unimproved, 50 per cent of the slightly improved and 7 per cent of the much improved received collapse therapy. All of these constituted 27 per cent of the 296 cases. Thus, a total of 49 per cent of the group received some form or combination of forms of collapse therapy, and roughly one-third, or 17 per cent, secured cavity closure thereby.

Finally, using all forms of treatment in 296 cases with cavity, an excellent result was obtained in 39 per cent (closure), and a good result in an additional 25 per cent (much improved).

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### INCIDENCE OF RHEUMATIC FEVER IN NEW YORK CITY HOSPITALS.\*

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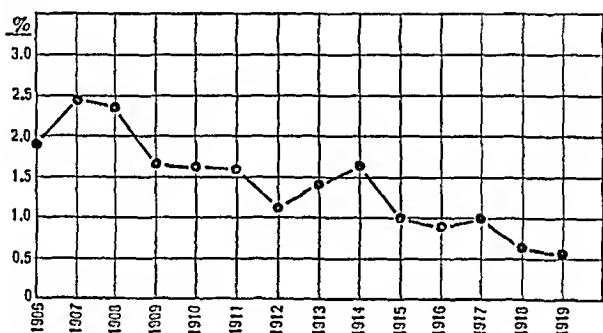
It has been noted by a number of physicians that there were fewer cases of rheumatic fever on the wards in the general hospitals after the World War than there had been previously. The present survey was undertaken to determine the truth of this statement as well as the underlying cause. It was hoped to obtain some information concerning the incidence of the disease and the effect of various conditions, such as the removal of infection, on the morbidity of rheumatic fever in this city.

Such an investigation is necessarily fraught with many difficulties and inaccuracies. The change of fashion as to what constitutes

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a diagnosis of acute rheumatic fever, the ever changing house staff and attending staff, and the incompleteness of records in the early days, are some of the points which must be considered before reaching a conclusion. In order to minimize the errors due to the first difficulty, *i. e.*, the difference in terminology of diagnosis, the charts of all the cases diagnosed as acute rheumatic fever, acute polyarthritis and acute arthritis have been examined. Only those cases were included in this series which had fever and an inflammatory arthritis affecting two or more large joints and usually showing cardiac manifestations. It was also thought that limiting the study to two hospitals, where the respective attending staffs had been present for a rather long period, would further minimize this difficulty.

Similar studies have already been reported by many other investigators, but the results are not in agreement. Alexander Lambert<sup>1</sup> published a paper in 1920 on the incidence of acute rheumatic fever

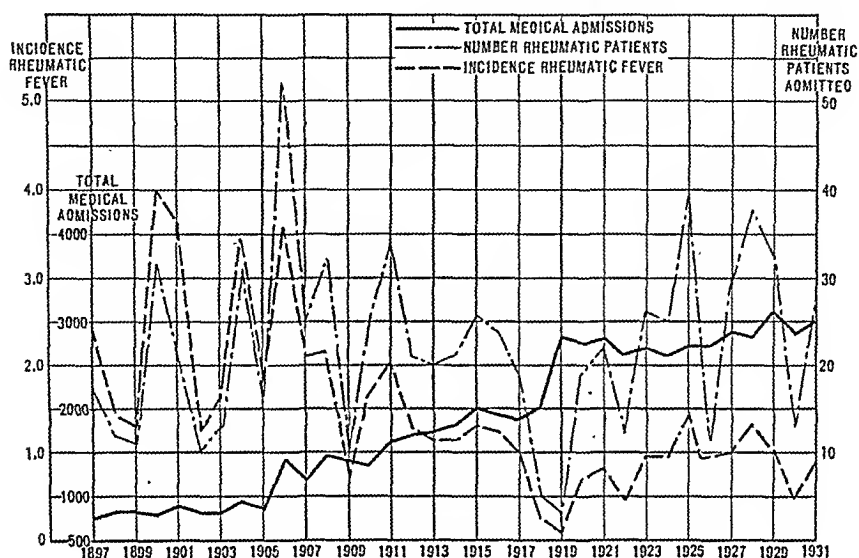


GRAPH 1.—Incidence of acute rheumatic fever.

at Bellevue Hospital. He reviewed the data of the cases from 1906 to 1919 and called attention to the steady decline in the number of cases. This decline, which is illustrated in Graph 1, was attributed by Lambert to the increasing removal of foci of infection, particularly due to the prevalence of better dental hygiene.

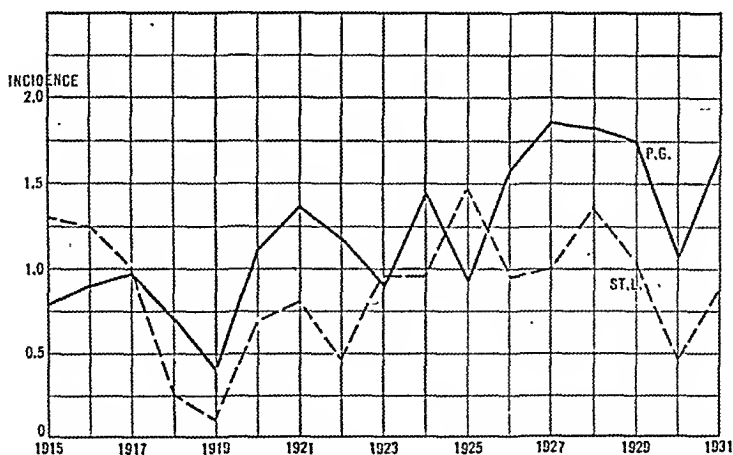
Poynton<sup>2</sup> began his book, "Recent Advances in the Study of Rheumatism" (1931) by saying "rheumatic fever in the clinical form would seem to be on the wane." On the other hand, in 1924 Ingberman and Wilson<sup>3</sup> concluded a paper by stating that "the general progress in preventative medicine and hygiene in the last twenty-five years has not seemed to influence the clinical course of rheumatism as we see it today." The latter investigators studied 185 cases of rheumatic fever, 88 per cent of which had their tonsils removed. Recurrences of rheumatic manifestations were observed in 75 per cent of the tonsillectomized patients in from 1 to 11 years. In the control group of 97 cases studied over a similar period, 80 per cent showed recurrence of rheumatic manifestations.

Kaiser,<sup>4</sup> however, throws a ray of hope into that dark outlook. In his investigation, 48,000 school children were divided into two groups; 20,000 who had had their tonsils removed at least 5 years



GRAPH 2.—Acute rheumatic fever (St. Luke's Hospital).

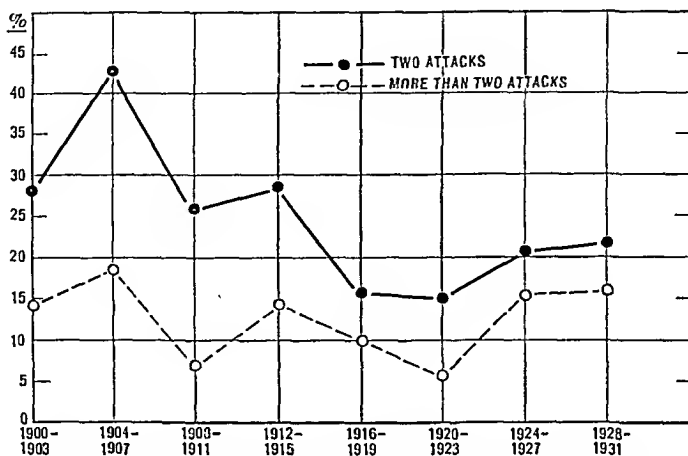
previously and 28,000 upon whom the operation had not been performed. At first sight the incidence of rheumatism did not seem



GRAPH 3.—Incidence of acute rheumatic fever (Post-Graduate and St. Luke's Hospitals).

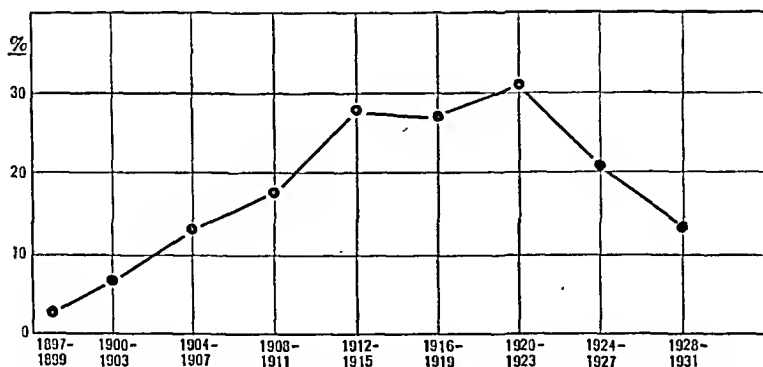
to be much influenced by the operation, since it occurred in 8 per cent of the tonsillectomized children and in 10 per cent of the non-tonsillectomized. Recurrent attacks of rheumatic fever, however,

were decidedly less common in the group who had had their tonsils removed and the incidence of carditis following chorea was also definitely diminished.



GRAPH 4.—Incidence of recurrent attacks (St. Luke's Hospital).

Of the 20,000 tonsillectomized children, 450 were suffering from rheumatic heart disease, while 817 were similarly affected among the 28,000 who still retained their tonsils. More significant was the discovery that in 478 cases of carditis the condition had developed in 83 per cent before operation, whereas it appeared as a first manifestation after enucleation of tonsils in only 179.

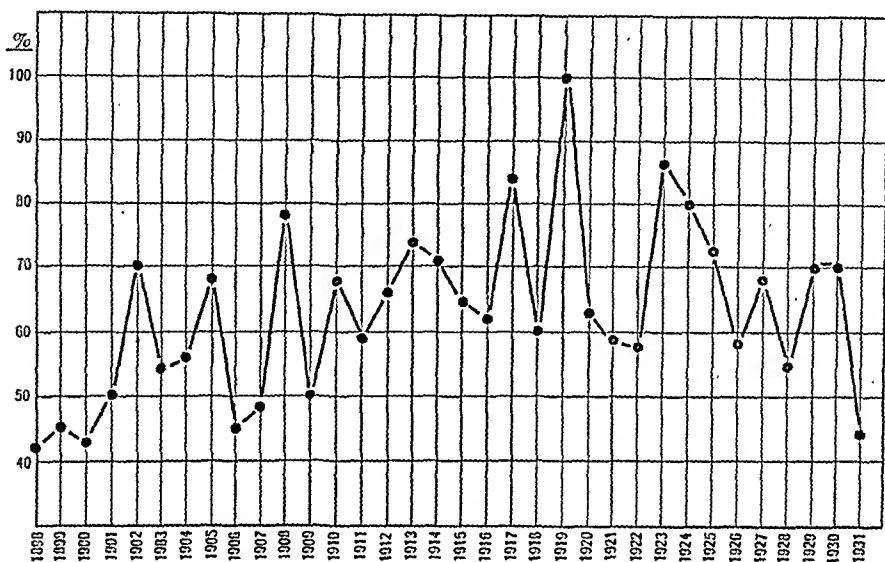


GRAPH 5.—Incidence of acute rheumatic fever with temperature of 104° F. or higher (St. Luke's Hospital).

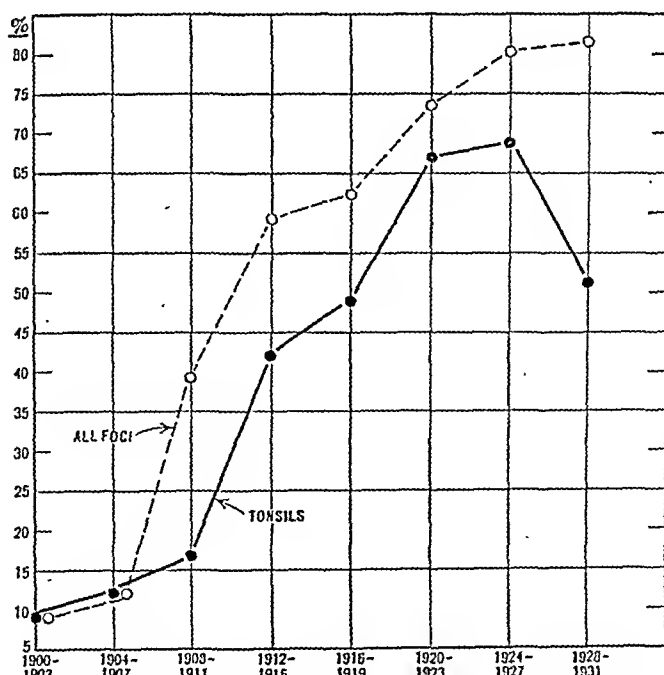
It is unnecessary to make an extended survey of the literature here. Suffice it to say that the expressed opinion on the question of the incidence of rheumatic fever is varied and contradictory. This is at least partly due to the incomplete statistical analyses which have served as their basis.



In the present series the records of 787 cases of acute rheumatic fever at St. Luke's Hospital and of 365 cases at the New York Post-Graduate Hospital have been studied. Since 1898 there have been

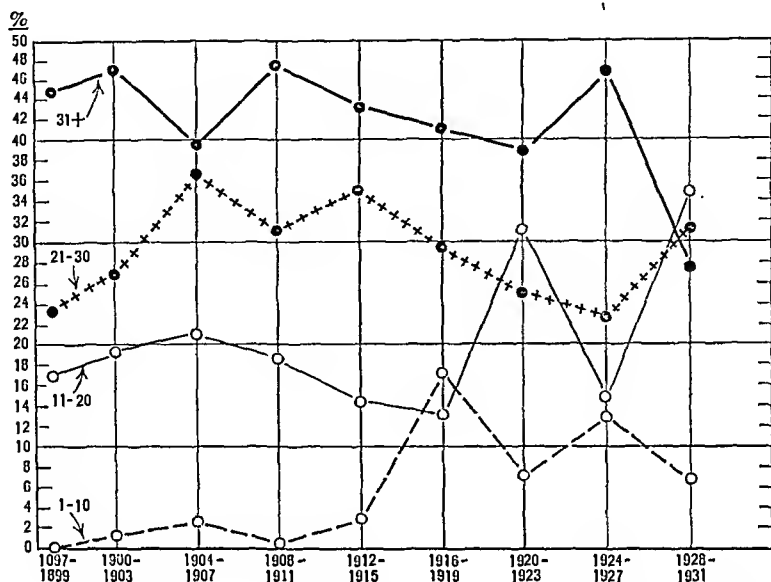


GRAPH 6.—Incidence of cardiac disease in acute rheumatic fever (St. Luke's Hospital).



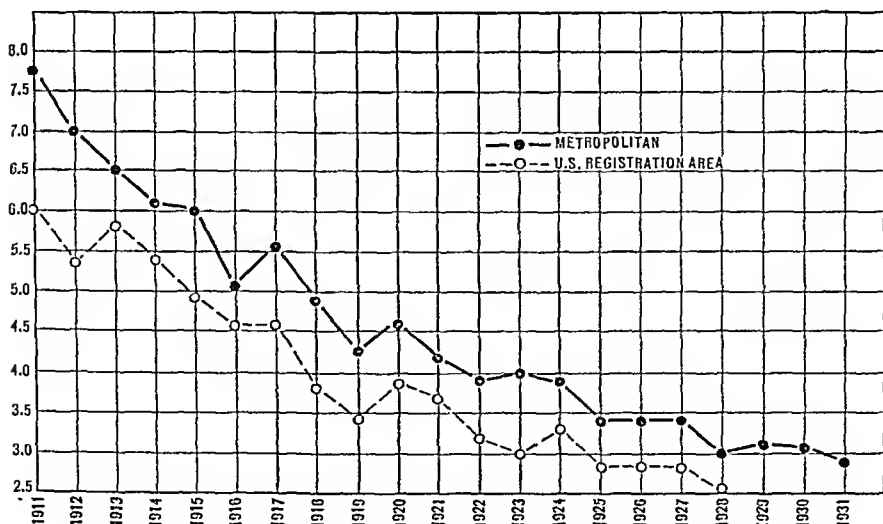
GRAPH 7.—Incidence of focal infection (St. Luke's Hospital).

wide fluctuations in the number of admissions of patients with rheumatic fever to the two hospitals under investigation. In spite



GRAPH 8.—Incidence of rheumatic fever according to age (St. Luke's Hospital).

of the variable incidence there appears to have been a steady decline both in the absolute number of admissions of rheumatic fever

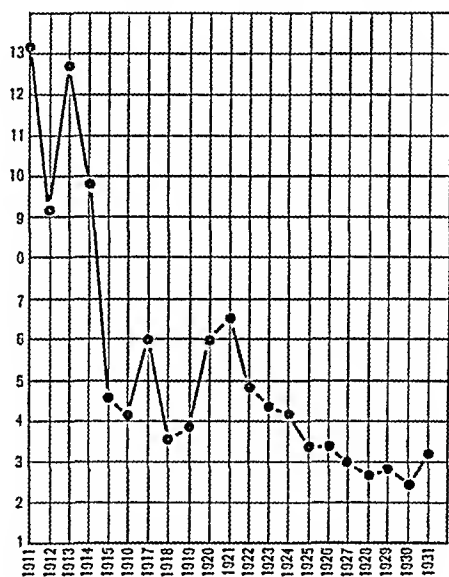


GRAPH 9.—Death rates per 100,000 from acute rheumatic fever.

cases and in the relative number, *i. e.*, as compared with other diseases. This condition lasted until 1919, since when there has

been a slow increase in both absolute and relative number of admissions. Graph 2 shows the incidence of acute rheumatic fever at St. Luke's Hospital from 1897 to 1931. On this graph is also plotted the annual number of medical admissions and the actual number of rheumatic fever admissions. Graph 3 indicates the incidence of acute rheumatic fever at St. Luke's and New York Post-Graduate Hospitals, located in different parts of New York City. The similarity of these curves suggests that a study made in either of these hospitals might give a fair idea of the average occurrence of the disease in this city.

Although the disease still occurs in a severe form, recurrences are less liable to occur now than formerly (Graph 4). In studying the charts of the earlier years, however, one is impressed by the rela-



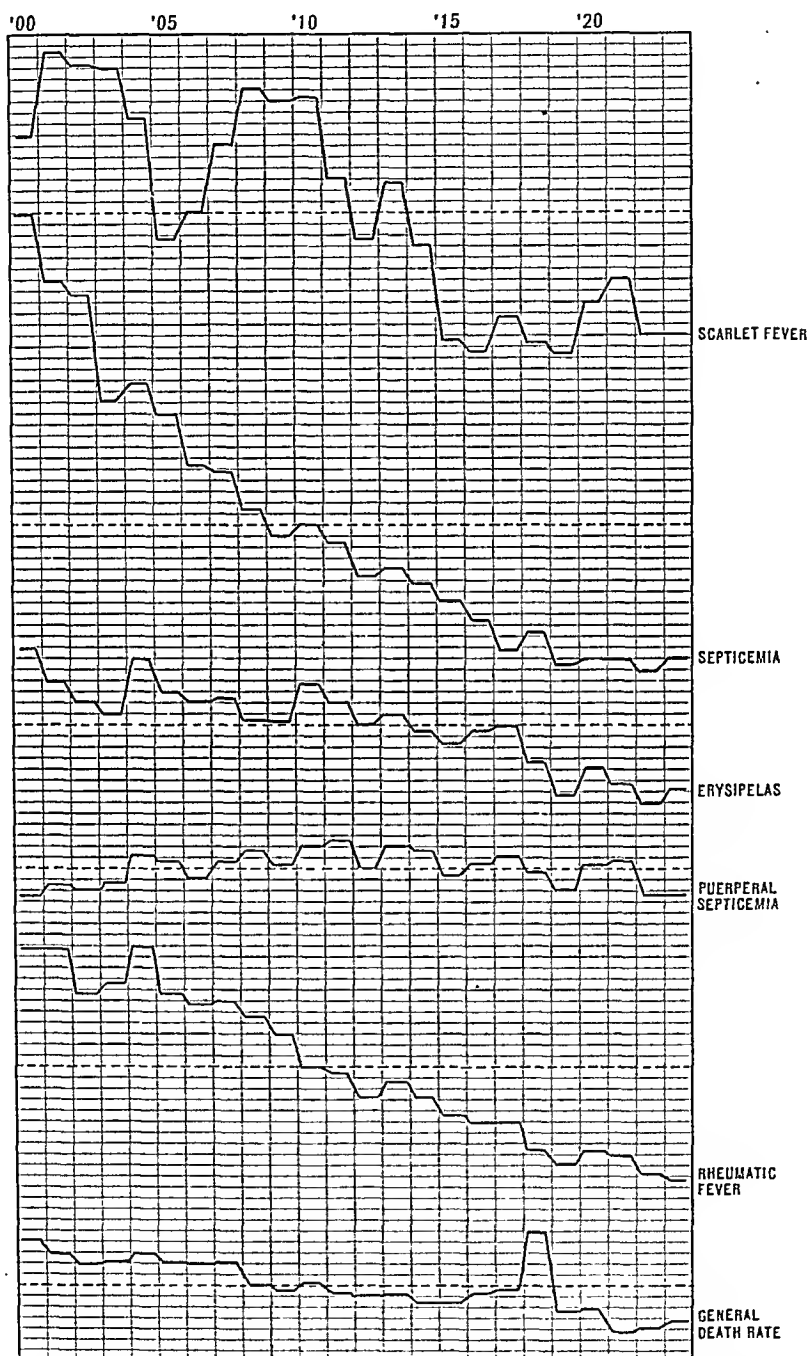
GRAPH 10.—Death rate from scarlet fever.

tively greater intensity as evidenced by the complication of pericarditis and the number of patients in whom the temperature rose above  $104^{\circ}$ . It is apparent from Graph 5 that there was a steady increase in the percentage of cases in which the temperature was  $104^{\circ}$  or greater until about 1923. In the last 6 years there has been a definite fall.

Graph 6 presents the curve for the incidence of carditis in acute rheumatic fever. It fluctuates considerably, but shows on the whole a tendency to rise until about 1919. After that there is a drop in the general slope of the curve. The graph for the cases from the New York Post-Graduate Hospital is again similar to that for St. Luke's, so we have not reproduced it here.

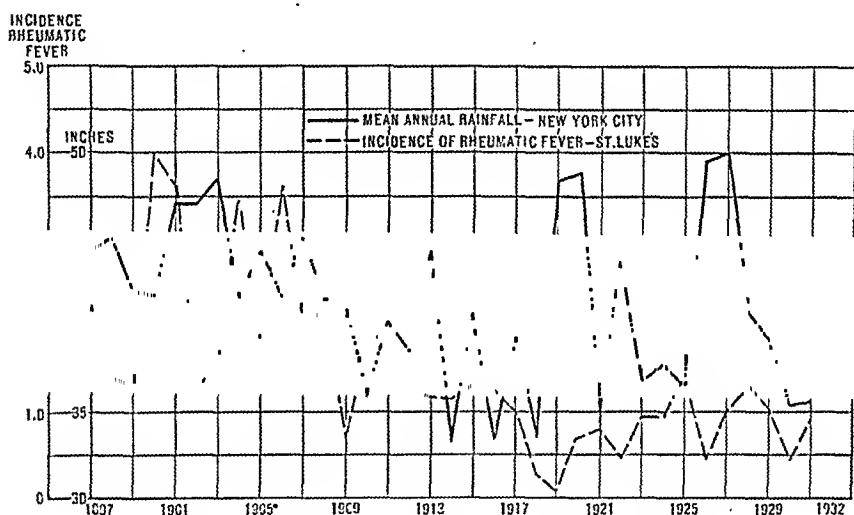
It is obviously impossible to take into account all the conditions

affecting the incidence of the disease, but four possible points suggest themselves as being of primary significance.



GRAPH 11.—A comparison of the death rates in the U. S. Registration Area from scarlet fever, septicemia, erysipelas, puerperal septicemia and rheumatic fever for the period 1900-1923.

FIRST. *The Problem of Removal of Foci.* There has been an increasing tendency in recent years to look for and remove foci of infection. Graph 7 shows the great increase of foci found and removed at St. Luke's Hospital since 1900. If the presence of foci is an important factor in the general susceptibility to rheumatic fever, then one might expect a graph for the frequency of this disease to be the reverse of that for foci found and removed, with a lag of several years in the former. In other words, a great increase in the detection and treatment of foci would be reflected several years later in a decreased incidence of rheumatic fever. But when Graphs 2 and 7 are compared we find a gradual decrease, with fluctuations, in the incidence of rheumatic fever until 1919, with a coincident steady rise in the removal of foci. This rise continues, but the inci-



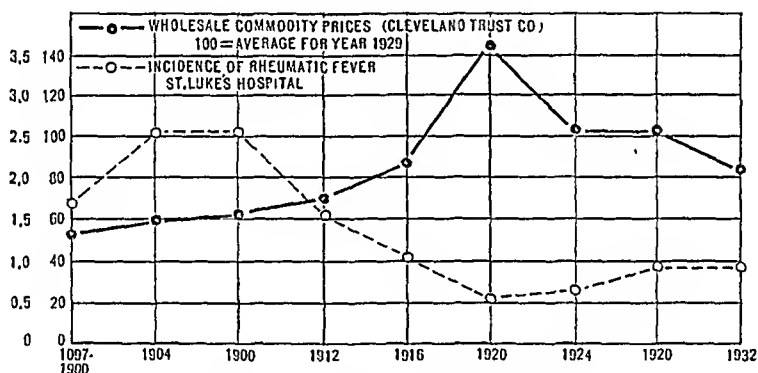
GRAPH 12.—Relation of moisture to rheumatic fever.

dence of rheumatic fever also increases. Although there has been a recent drop in the frequency of tonsillectomies, it cannot be held responsible for the increase in rheumatic fever, because this increase began before the drop in tonsillectomies. Our graphs, then, do not permit us to conclude that the removal of foci of infection has any significant effect on the incidence of rheumatic fever.

The variations in the number of cases of rheumatic fever in the different age groups have been presented in Graph 8. The patients were divided into four groups: 1 to 10 years, 11 to 20, 21 to 30, and 31 and over. Inspection of the curves leads to the conclusion that in the older groups the disease shows a greater tendency to decrease in recent years than in the younger groups. This might possibly indicate that the older people are now deriving some benefit from

removal of foci at earlier ages, except that we have seen from Graph 7 that the relation of the presence of foci to rheumatic fever is very doubtful.

SECOND. *The Possible Cyclical Character of Rheumatic Fever.* It has been said that rheumatic fever follows a cycle similar to that found in many acute infectious diseases. The rapid fall in the mortality of acute rheumatic fever from 1911 to the present is seen in Graph 9. These curves were supplied by Mr. Van Buren, statistician of the Metropolitan Life Insurance Company. Not only is there a rapid fall in the mortality, but the curve may be considered to be made up of four fairly similar cycles of 3 to 5 years each, characterized by a sharp rise and subsequent gradual and more prolonged fall. Graph 10 shows a fairly similar mortality curve for scarlet fever. Whether the similarity of the curves indicates a changing degree of virulence of the infection or whether it indicates improving hygienic conditions which are reflected in decreasing susceptibility



GRAPH 13.—American business activity.

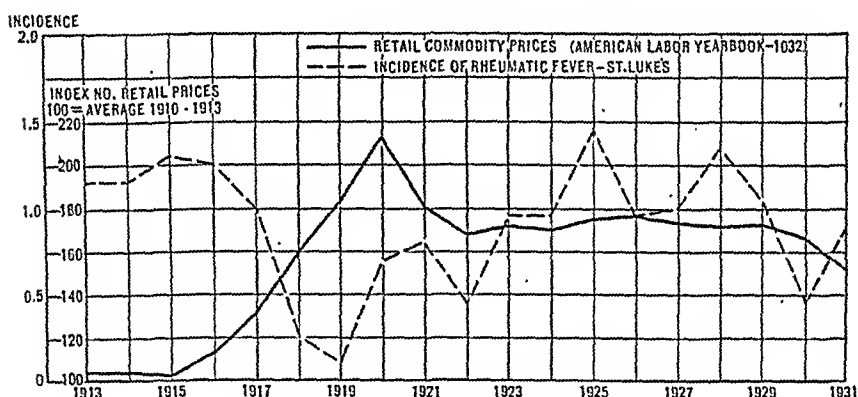
to infection is difficult to say with the data at hand. It is equally probable that the changes in mortality of the two diseases do not have a similar cause at all.

Graph 11 is reproduced from a paper published by Atwater<sup>3</sup> in 1927 on the epidemiology of acute rheumatic fever and related diseases in the United States based on mortality statistics and covering the period 1900 to 1923. He concluded that the history of the disease in the United States during the past half century showed a striking decline in the number of deaths and probably in the number of cases as well. The graph shows the parallelism between the proportion of deaths due to rheumatic fever and to streptococcal diseases, and the apparent cyclic character of these diseases.

THIRD. *The Question of Rainfall.* The disease is more prevalent in periods of greater rainfall. It is well known that rheumatic

fever is a disease of cold, damp countries, occurring mostly along the coast, river bottoms and canals. This fact suggests that years of increased rainfall might be marked by an increase in the incidence of acute rheumatic fever. This relationship is shown in Graph 12. The average annual rainfall was taken from the figures of the weather bureau in New York City.<sup>6</sup>

If it is true that rheumatic fever is more liable to occur in wet weather, then a rise in the rainfall curve ought to be accompanied by the curve for the incidence of rheumatic fever within the following year. When we examined the rheumatic fever curve after the seven rainiest years, we found a rise in 6 instances, whereas after the 7 driest year there was a subsequent drop in 4 instances, a rise in 2 and no change in 1. It seems justifiable to draw the conclusion that wet weather is one of the factors increasing the prevalence of rheumatic fever. In contradiction to this conclusion, Newsholme<sup>7</sup>



GRAPH 14.—American business activity.

has reported that in England there is an increase in rheumatic fever in dry years, and he attributed this to the increase in the amount of dust and the consequent greater ease of spreading infections.

FOURTH. *The Question of Economic Status.* Acute rheumatic fever seems to be a disease of the poorer classes and would therefore be more liable to be widespread at times when more people are deprived of adequate food, clothing, fresh air and medical attention. It is almost impossible to choose a satisfactory index for the general cross-sectional economic welfare of the inhabitants of New York City. Since there are no reliable statistics on the number of unemployed, it would be very inaccurate to use average weekly earnings. The income tax report is likewise unsatisfactory because it gives no idea of the economic fluctuations of the large group who do not pay a tax and with which we are mainly concerned. In

this study we have first plotted the curves for the wholesale commodity prices (Graph 13), which give a fairly good index of business activity. Graph 14 shows the fluctuations in the average retail prices of 30 basic commodities, and from this some idea of the variation in the cost of living can be gained. In both these graphs the important points to be observed are the rise in economic activity until 1920 which was followed by a sharp fall and the next period of stability which was broken by the crash of 1929. If we attempt to correlate with this the curve for the incidence of rheumatic fever we find that a fairly good reciprocal relationship manifests itself in Graph 13. In the more detailed graph (Graph 14), the correlation is not so uniform. It is true that the incidence drops during the first period of "prosperity," but it had already begun to rise before the 1920 depression was well under way. Inspection of the graph reveals other definite discrepancies and, on the whole, hardly seems to lead to the conclusion that fluctuations in economic welfare and the morbidity of rheumatic fever go hand in hand. The statistics for this year, however, will be interesting in this connection because of the sharp rise in unemployment and distress in the lower middle class group.

**Summary.** 1. There has been a decline in the incidence of acute rheumatic fever at both St. Luke's Hospital, New York and the New York Post-Graduate Hospital from 1897 to 1919 and a rise since that time.

2. Four possible factors have been discussed with reference to this changing incidence: (a) Removal of foci of infection; (b) Cycles in the virulence of infectious diseases; (c) Rainfall; (d) General economic conditions.

The author wishes to express his appreciation to Dr. Lewis F. Frissell who suggested this survey and to Dr. Walter Lough for his suggestions and help.

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## GASTRITIS IN ITS RELATION TO OTHER DISEASES.\*

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GASTRITIS, which may be defined broadly as a diffuse degenerative or inflammatory disease of the mucosa of the stomach, was looked upon during the latter part of the past century as the common cause of indigestion and responsible for many other ills of the body. With the discovery that the microscopic mucosal changes described by the pathologists of that time were due to postmortem autolysis and with the coincident popularization of the stomach tube, attention gradually shifted to the secretory disturbances of the stomach. Even the advanced types of chronic gastritis, recognizable by gross atrophic and hypertrophic changes, lost their interest for the pathologist and clinician, and for a time no attempt at correlation of the anatomic and secretory alterations was made. Although Faber and Lange,<sup>1</sup> in 1908, making use of a technique introduced 18 years before by Hayem for prompt fixation of the gastric wall at death, described minute inflammatory changes of the stomach mucosa that were associated with achylia, their work attracted relatively little immediate attention. This was probably due, in part, to the fact that at the same time gastric ulcer, gall bladder disease, and appendicitis were being recognized as frequent causes of indigestion. Even now, in spite of the great interest in the gastric secretory disturbance demonstrated by Castle<sup>2</sup> as responsible for Addisonian anemia, some of the textbooks on pathology entirely neglect the subject of gastritis, and at most autopsies only a brief note on the gross appearance of the stomach is made.

Faber,<sup>3</sup> however, has continued to emphasize the significance of gastric inflammatory changes in relation to disturbances of stomach secretion. He considers that a mild or localized gastritis may exist with the acid secretion intact or even increased, while any diffuse form, especially that with advanced glandular atrophy, leads to a marked reduction or absence of such secretion. Orator<sup>4</sup> and Konjetzny,<sup>5</sup> basing their work chiefly on the study of resected specimens, have arrived at much the same conclusions. Hurst,<sup>6</sup> who like Conner<sup>7</sup> and Wilkinson<sup>8</sup> believes in an hereditary or constitutional factor in the development of achlorhydria in some instances, insists that it is usually explainable on the basis of a gastritis. He has demonstrated that often a recovery of acid secretion may be

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obtained by hydrogen peroxid lavage, even occasionally when the histamin test has been negative, and considers this as strong evidence in favor of the gastritis being primary. He has observed cases of pernicious anemia with achlorhydria in which the onset of symptoms dated from an acute gastritis. Additional support for the contention that gastritis leads to a loss of acid secretion is found in the rising incidence of achlorhydria with age. A lack of mucus in the gastric contents, which usually is present with achlorhydria, does not eliminate gastritis as the causative factor, because in the advanced atrophic stage no secretion whatever may be possible. Finally, from the clinical viewpoint, I have observed many cases of achlorhydria in which roentgenologic study showed the typical signs of hypertrophic gastritis.

From the point of view of the pathology involved it may be said that while those especially qualified to speak, such as Faber, Konjetzny, Orator, and Hillenbrand,<sup>9</sup> are by no means in entire agreement as to the anatomic criteria which separate the borderline cases into normal and abnormal groups for certain age periods, it does seem clear from their investigations that a so-called chronic gastritis consisting of an extensive glandular atrophy, often with gland change to the type of the small intestine, an increase in follicular centers, round cell infiltration between the glands, and eventually destruction of the glandular structures with overgrowth of fibrous tissue frequently occurs, particularly in persons past middle life. These changes may be present in either of the gross types of chronic gastritis, usually referred to as hypertrophic and atrophic.

My interest, aroused in this subject some years ago, has been intensified by Castle's researches and Hurst's clinical observations. For 2 years W. O. Abbott, of our clinic, has been injecting with formalin solution the stomachs of patients dying in our wards and securing specimens from such of them as came to autopsy; these, with resected specimens obtained at the operating table, he has subjected to careful microscopic study. His work will be reported in detail separately, but I may say here that it tends to support the contention that chronic gastritis and achlorhydria are usually associated.

Although it is still impossible to state with certainty which is primary, the gastritis or the secretory dysfunction, the mere fact of their common association justifies consideration of chronic gastritis in its relation to some of the other diseases in which achlorhydria is usually found. These are Addisonian anemia, other anemias of the chlorotic or microcytic type, subacute combined degeneration of the spinal cord, carcinoma of the stomach; sometimes diarrheal diseases, such as sprue; less frequently diseases of the gall bladder, arthritis, etc. The achlorhydria itself has not been proved to be of etiologic significance in any of these diseases, but it is reasonable to assume that the lack of hydrochloric acid

may be only one evidence of an altered mucosa, and that other associated disturbances, such as a lack of the intrinsic factor of Castle in Addisonian anemia, may be on a similar organic basis.

**Relationship to Other Diseases.** Since, then, a so-called chronic gastritis, consisting of more or less diffuse degenerative and inflammatory changes, and usually characterized clinically by a hypochlorhydria or an achlorhydria, is recognized, we are prepared to consider in relation to this disease of the stomach some of the other diseases with which achlorhydria is commonly associated. I shall refer at this time to only two of them: gastric carcinoma and Addisonian anemia.

(A) *Gastric Carcinoma.* With the exception of the cases that are secondary to ulcer (probably not more than 10 per cent) and those that are secondary to benign polyp (probably not more than 5 per cent) we have had in the past no very clear conception regarding the predisposing factors in the production of gastric cancer. For the majority group, however, including those on a polyp basis, and in definite contrast with those on an ulcer basis, two clinical facts stand out prominently: (1) that they usually present no pre-cancer symptoms, and (2) that an achlorhydria is commonly present. The absence of a previous gastric history has been responsible for the idea, still in vogue, that this type of carcinoma springs *de novo* from a normal gastric wall, but the associated achlorhydria is not consistent with such a theory. This becomes manifest when attention is directed to the following considerations:

1. The patients who are believed to have developed cancer on a stomach ulcer basis show no progressive decrease in gastric acidity, this indicating that the achlorhydria is not a secondary development. We have usually found free acid in our cases that gave a long ulcer history, no matter what the stage of the malignant process. Hurst had 3 such cases followed for a considerable period of time, and found no decrease in the acidity; he has not seen a case in which acid was once present and later in the disease disappeared. In 12 of 14 ulcer-cancer cases reported by Orator,<sup>4</sup> and in 9 cases reported by Stewart<sup>10</sup> in which acid was at one time present, it persisted to the end. Pollard and Bloomfield<sup>11</sup> report 2 ulcer cases in which the acidity was higher after the secondary development of cancer.

2. On the other hand, the achlorhydria usually found in the majority group, those with a short history and nothing to suggest a preceding ulcer, has been demonstrated in a few cases before the development of cancer. Hurst<sup>6</sup> has cited a case that had achlorhydria 2 years before the development of recognizable cancer; Alexander,<sup>12</sup> 1 with achlorhydria 26 months before; Veale,<sup>13</sup> 1, 3 years before; Porges,<sup>14</sup> several, for years before. The scarcity of such reports is not surprising since gastric analyses are rarely done on patients without gastric symptoms.

Furthermore, it is now appreciated that carcinoma of the stomach not infrequently develops in patients the subject of Addisonian anemia, such patients almost always having had an achlorhydria for a long time. We have had at least 3 instances of gastric cancer in pernicious anemia cases, and Hurst<sup>6</sup> has reported 5 such cases. In 1 of his cases the carcinoma developed 9 years after onset of the anemia and 4 years after its cure by the use of liver. In this case a partial gastrectomy was done and a section from the unaffected fundal portion of the stomach was removed for study: this showed atrophic glandular changes. Hurst has also referred to the relatively high incidence of carcinoma of the stomach and of pernicious anemia in different members of the same family. The age and sex incidence for the two diseases is also much the same.

3. The prognosis after operation in the gastric cancer cases with free hydrochloric acid is no better, in fact not so good, as in those with achlorhydria. This is our own impression, is confirmed by Hurst, and is the experience of other clinicians. It would be the reverse if the achlorhydria were a secondary development and so indicative of more advanced malignant change.

Thus, it seems clear that the achlorhydria present in the majority of cancer of the stomach cases cannot be attributed to the cancer itself. Since, however, we have presented evidence to indicate that such achlorhydria is usually associated with chronic gastritis and that such gastritis ordinarily gives rise to no symptoms, an antecedent gastritis may be considered as an explanation for the lack of hydrochloric acid.

In this connection our reference to the fundus specimen secured by Hurst in a case of pyloric cancer, and which showed atrophic changes, assumes significance. Furthermore, Konjetzny and Salzman<sup>6</sup> have showed histologic transitions from chronic gastritis to cancer. According to Bloomfield and Pollard,<sup>15</sup> Lebert, in 1878, found in 41 of 56 cancer cases an extensive gastritis, even at a distance from the growth, and was the first to point out the relationship. Orator,<sup>4</sup> by more modern methods, has demonstrated to his satisfaction such a lesion in 19 of 20 so-called "primary" carcinomatous cases, whereas in ulcer-cancer such gastritis as he found was localized about the malignant lesion only, usually in the pyloric end of the stomach, and did not involve the fundus.

Abbott, of our clinic, has had in his series of stomach specimens 11 from cases of gastric cancer: in 4 an achlorhydria had been demonstrated by fractional or histamin test; in 3, the free acid was within normal limits, and in 4 no gastric analysis had been made. Of the 4 with achlorhydria all gave a short history, averaging 8 months; while the duration of digestive symptoms in the 3 cases with acid was respectively 13 months, 5 years, and 42 years. In only 2 of the cases, both with achlorhydria, did he have the entire stomach, and in both of these an extensive atrophic gastritis

was present; the others, including those with free acid, also showed atrophic or hypertrophic gastritis, but only the parts of the stomach near the malignant lesion were available for study.

Eliason and the author<sup>16</sup> found evidence of gastritis, usually hypertrophic, in our 8 cases of polyp-cancer, though in some instances the malignancy was just beginning: in all of them an achlorhydria was present.

Thus certain data are available to indicate that a gastritis, responsible for achlorhydria, has preceded some cases of gastric cancer, and probably such a lesion, unrecognized, has been present in many more.

(B) *Addisonian Anemia*. Equally interesting is the consideration of primary pernicious or Addisonian anemia in connection with gastritis. Even before the demonstration by Calin and von Mering<sup>17</sup> in 1886, that achlorhydria was usually associated with this type of anemia, atrophic changes in the gastric mucosa were demonstrated by Fenwick<sup>18</sup> in this disease. He, together, with Quincke, Nothnagel and Ewald, who also called attention to the relationship, regarded the gastritis as primary. The earlier references to the stomach alterations must now be disregarded, however, due to doubt concerning postmortem effects; but, in 1900, Faber and Bloch,<sup>19</sup> using an acceptable technique, described extensive changes in the gastric mucosa of 2 patients dying of this disease: a diffuse inflammation leading to destruction and atrophy of the glands, most severe in the cardia and decreasing toward the pylorus. They were inclined to believe, at that time, that the gastric affection and the blood changes were in common due to a toxic or infectious cause.

Hérzberg,<sup>20</sup> in 1911, after a very careful study of the stomachs of primary anemia cases, in many of which she found a severe atrophy of the mucosa, inferred that it was improbable that the gastritis was primary. She admitted, however, that the gastric changes often were found in the early stage of the anemia, and found no such changes in the secondary anemias. She also believed that the gastric and blood changes were due to the same cause.

It is probable, unless it becomes possible to produce pernicious anemia experimentally, that a determination as to which, the anemia or the gastritis, is primary can never be made on purely pathologic-anatomic grounds. Sections from the stomachs of persons who later develop pernicious anemia are not likely to become available for microscopic study. On a clinical basis, however, we now have reason to believe that the gastritis appears first.

This conclusion is based, in the first place, on the observations of many workers that achlorhydria, which certainly is the outstanding clinical sign of gastritis, frequently precedes the development of pernicious anemia. Faber and Gram,<sup>21</sup> Sturtevant,<sup>22</sup> Riley,<sup>23</sup> and Conner<sup>7</sup> had cases that showed an achlorhydria from 4 to

25 years before the development of pernicious anemia. Moschcowitz<sup>24</sup> especially has claimed that because it exists throughout the disease, does not disappear during remissions, and has been found so often to precede the onset of the anemia, the achlorhydria must be looked upon as primary.

Secondly, pernicious anemia not infrequently occurs in persons in whom the diagnosis of chronic gastritis has previously been made. Hurst<sup>6</sup> refers to its development in 4 patients who were chronic alcoholics, and in 1 of these he observed a return of acid after treatment of the gastritis. In 3 other cases of pernicious anemia, believed to have developed on the basis of a gastritis, he got a return of acid after treatment, this suggesting that the gastritis was not of the completely atrophic type. Torrey<sup>25</sup> tells me of 3 of his cases of alcoholic gastritis that late in the disease presented the picture of this type of anemia together with marked cord changes. I have had 1 such case on an alcoholic basis in which a small amount of free acid was demonstrable: the anemia responded readily to liver therapy.

Finally, roentgenologic study sometimes demonstrates an advanced hypertrophic type of gastritis in pernicious anemia cases. In our last 27 cases so studied, 7 showed such marked hypertrophy of the gastric rugæ that it seems impossible that it could have developed within the time that the patients had been anemic.

Similarly suggestive of the primary importance of gastric mucosal changes in Addisonian anemia, and of even more immediate interest, is the clean-cut demonstration by Castle<sup>2</sup> that the absence of an intrinsic factor, normally secreted by the stomach, causes the disease. Such a secretory disturbance, like the achlorhydria, can most easily be explained on the basis of an anatomic change in the gastric wall.

**Conclusions.** 1. Chronic gastritis, manifested clinically by a decrease or absence of hydrochloric acid and sometimes by the presence of mucus in the gastric contents, is commonly found in association with carcinoma of the stomach and Addisonian anemia.

2. Evidence is presented to indicate that such gastritis usually precedes the development of these diseases and is a factor in their origin.

3. Since the etiology of chronic gastritis, its various forms and the means of recognizing it clinically are not understood, it is obvious that if we are to prevent its development and the diseases for which it seems to be responsible, much experimental and clinical investigation is clearly indicated.

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## THE REDUNDANT DUODENUM.

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ANOMALIES of the duodenum are not infrequently observed in the routine roentgenologic examination of the gastrointestinal tract. In recent years greater attention has been directed to this portion of the bowel, and abnormalities have been commonly noted which have hitherto escaped recognition. Anomalies of the duodenum are much more common than a survey of the literature indicates. Clinically, but little attention has been directed to these conditions up to a comparative short time; but considerable importance is now attached to them especially in regard to their etiologic relationship to the production of digestive symptoms. Recent literature abounds with individual case reports of various anomalies of the duodenum, which have been especially discovered as a result of a more thorough roentgenologic investigation. Such cases are, however, rarely recognized by any other method of examination. Most of these findings cannot be termed as definite clinical entities and the clinical signs of this group are rarely distinctive or characteristic. The diagnosis must necessarily depend upon a painstaking Roentgen study.

Too often, however, these anomalies escape the observation of the

roentgenologist and thus remain undetermined. It is probably true that with better Roentgen technique and more thorough investigations they will become more frequently recognized and their full significance brought to light.

The duodenum, about 10 inches in length, has a definite configuration in the shape of an incomplete circle or C-shaped, which under abnormal conditions may take on bizarre forms, such as the U-shaped, V-shaped and other distortions (Fig. 1).

The first part of the duodenum is the most mobile, but the remaining portions are practically fixed and bound down to adjacent viscera and to the peritoneum. The first portion of the duodenum, the most movable, is more or less fixed by the hepatoduodenal ligament, the free margin of the lesser omentum. A fold of the hepatoduodenal ligament extends down from the posterior surface of the gall bladder to the descending portion of the duodenum—the hepatocolic ligament. This ligament, however, is not constantly present. From the above description it is evident that the hepatoduodenal and hepatocolic ligaments play an important rôle in the fixation of the superior segment of the duodenum. These ligaments are responsible for the maintainance of the looping of the redundant duodenum.

In this study I desire especially to call attention to a redundant condition of the superior portion of the duodenum. This is an interesting anomaly which frequently passes unrecognized. During our routine roentgenologic study of the gastrointestinal tract I have encountered in a number of instances an elongation or lengthening of the superior portion of the duodenum. In all, a ptosis of this segment resulting in an abnormal loop was observed, which produced a puddling and retardation of the contrast meal like a water trap in which the passage of the opaque meal is somewhat blocked. The superior angle appears definitely fixed and displaced distally. In addition, the superior segment of the duodenum is fixed at its proximal portion, viz., at the junction of the first part or cap with the second part of the duodenum. The unusual lengthening of the superior segment results in a sagging, ptosis and looping, producing the characteristic picture of the redundant duodenum. The two fixed points in the superior portion are well illustrated in Figs. 1, 2 and 3.

Roentgenologically this elongated segment of the superior duodenum varies in length from 5 to 10 cm. Several types have been observed, such as the U-shaped, V-shaped, double looping and the serpentine forms. Occasionally only a sagging of the elongated segment is noted. These types are illustrated in Fig. 1.

Under normal conditions the Roentgen examination of the duodenum presents the first portion or bulb surmounted directly upon the pyloric outlet, which is directed upward, slightly to the right and somewhat posteriorly. This is commonly known as the superior



portion and is usually not more than 5 cm. in length. At the apex of the bulb or duodenal cap, the second portion is observed to form an angle with the first part and then descends downward to the right and posteriorly. No transverse elongation of this section of the duodenum is observed normally. The angulation of the superior portion is easily recognized and is more or less fixed by the hepato-duodenal ligament. From this angulation the descending portion seems to take a sudden drop. However, where the redundant duodenum is noted, this picture is quite altered into a marked elongation or lengthening of the superior segment. The duodenal cap is not

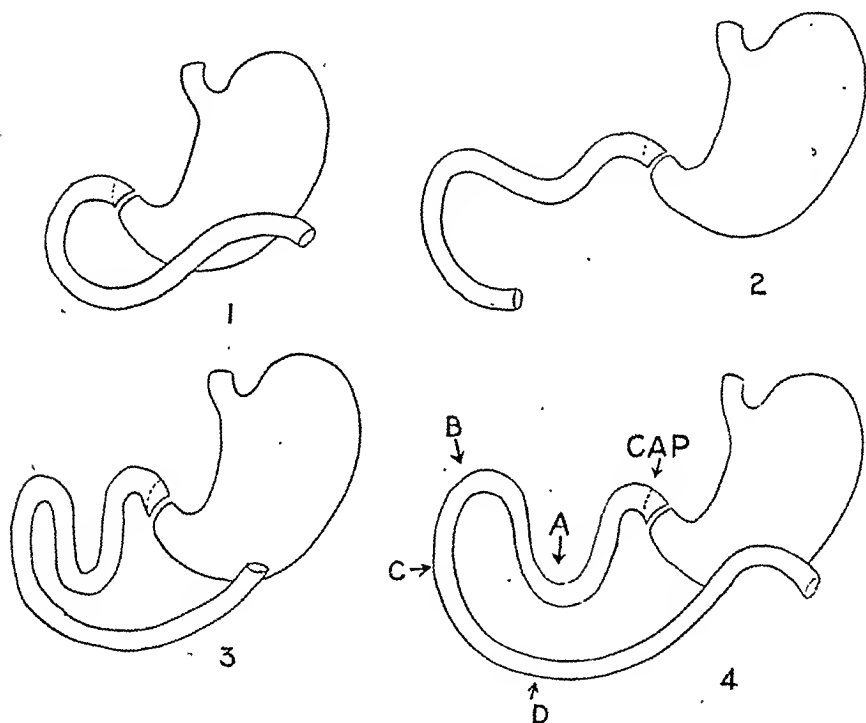


FIG. 1.—Diagrammatic drawing, illustrating the redundant duodenum. 1. Normal duodenum; 2, sagging elongated superior segment; 3, V-shaped, water trap effect of superior duodenum; 4, U-shaped, A, B, C, D, described in Fig. 2.

affected and seems to be normal in position and in size. In some instances at first glance the extra loop appears as an integral part of the cap which produces the appearance of an enlarged cap or diverticulum. This is due to the coalescing of the extra loop with the cap shadow, but upon manipulation no connection with it can be demonstrated.

*Redundancy of the Superior Duodenum and its Clinical Significance.* This form of anomaly has been variously described as ptosis, festooning or extra looping, terms which cannot be considered satisfactory. It is apparent that, since the duodenum is of greater

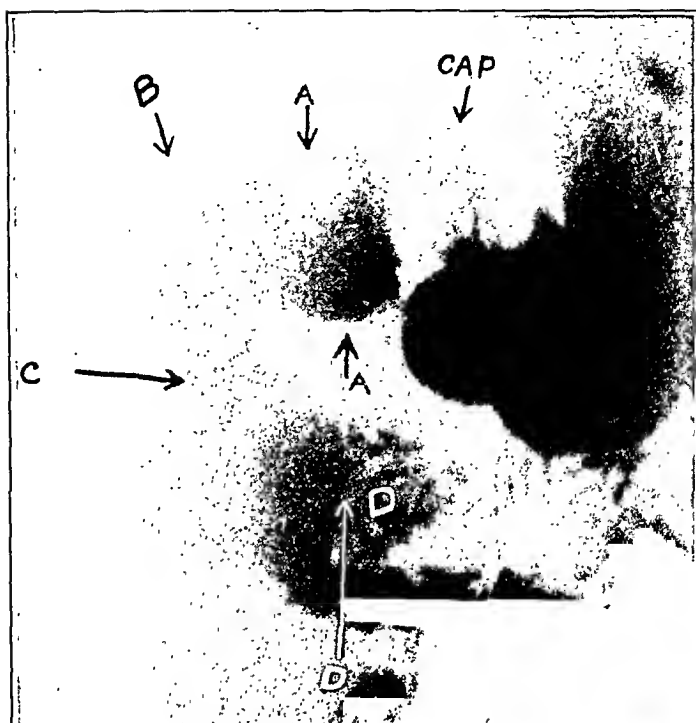


FIG. 2

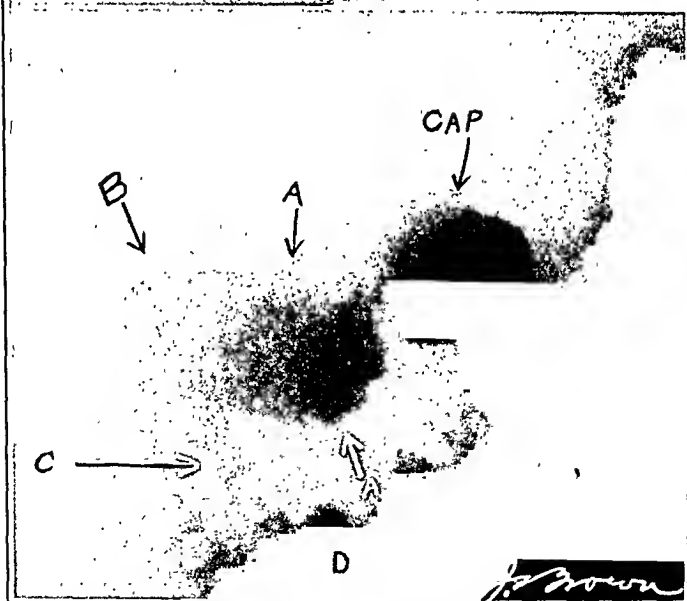


FIG. 3

FIG. 2.—The lengthened duodenum with looping at A. This also illustrates the two fixed points. 1, at cap, representing the hepatoduodenal fixation, and 2, at B, the hepatocolic fixation; C, descending duodenum; D, transverse portion.

FIG. 3.—The unusual length of the superior duodenum with the extra loop, or water trap at A is shown.

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length than normal, the term redundant duodenum should be adopted as being more accurate as well as descriptive, and fitting more definitely with such redundant affections of a similar type as, for example, the redundant colon.

The material selected for this study comprises a group of 10 cases, all of which present a definite elongation of the superior portion of the duodenum with sagging and looping of the segment. Increasing interest is now being attached to this anomaly due to its effect upon the motility of the duodenum and the production of a condition which may have considerable significance in the formation of ulcerations in this area. As a result of the diminished motility with consequent stasis as well as retardation and lagging as is revealed by the contrast meal, this factor may easily play an important rôle in the production of such disturbances. An early recognition of this anomaly is essential in order to establish effective treatment, which should be instituted early so as to eliminate the possibility of secondary complications which may readily occur. In the diagnosis, other factors simulating this anomaly must be borne in mind, such as adhesions of the duodenum secondary to a gall bladder infection.

The redundant duodenum must be regarded as a definite easily recognized roentgenologic entity. These cases rarely present any signs of gall bladder infection. On the other hand, in nearly every instance in this series a typical or atypical picture of an ulcerated duodenum was found. In some instances, even when the roentgenologic appearance of ulceration is absent, the clinical picture frequently is that of ulcer. The association of ulceration with this anomaly is very significant. In those instances in which ulceration was not found, Roentgen evidence of duodenitis was observed.

In this series of cases the Roentgen examination presented evidences of ulceration in 5 instances; duodenal in 3, pyloric in 1 and gastric in 1. Duodenitis was present in the remaining 5 cases. Duodenal stasis, lagging and retardation was observed in every instance.

It seemed of importance to determine whether the relative position of the stomach and colon had any definite relationship to that of the redundant duodenum. In 5 instances the position of the stomach and colon was observed to be normal; in 1 a slight ptosis was noted; in 1 a moderate ptosis and in but 3 was there marked ptosis of the stomach and colon. It may, therefore, be concluded, at least from these findings, that the position of the stomach and colon bears no special relationship to the redundancy of the duodenum.

The gastric acidity was normal in 3 cases; a hyperacidity occurred in 6 and an achylia in 1.

Age seems to be an unimportant factor. In this series the ages ranged between 26 and 57 years.

Sex. There were 8 males and but 2 females in our cases, indicating that the redundant duodenum is probably more frequent in the male sex.

The diagnosis is not, as a rule, possible from the history and physical findings and must be based largely upon a Roentgen investigation. Though the condition is best recognized under the fluoroscope, this anomaly may also be recorded on the films, when placed in the proper position. The fluoroscopic examination is usually best made with the patient in the upright posture, viewed anteroposteriorly, obliquely and laterally. Examinations should also be made routinely in the prone position. In the fluoroscopic examination one can manipulate the entire duodenum and especially bring into view the redundant segment, which may otherwise not be visible. Most frequently one observes a puddling in a loop hanging from the midsuperior portion of the duodenum, between the cap and the descending sections. As has already been stated this has the appearance of a water trap, which definitely retards the outflow of the contrast meal and which at once gives a clue as to the possibility of the presence of this abnormality. On manipulation this puddling entirely disappears, only to return on the next spurt of the opaque meal through the duodenum.

Roentgenologically a double fixation of the superior duodenum is presented in this group of cases, which is not due to acquired adhesions, but represents most likely a congenital anomaly. The fixation is due to the presence of peritoneal bands, represented by the hepatoduodenal and the hepatocolic ligaments. The presence of a redundant superior duodenum is best explained upon the basis of a congenital formation, in which the duodenum is lengthened, so that it cannot fit into the space allotted to it. This anomaly therefore seems to be dependent upon the unusual length and abnormal fixation of the superior portion of the duodenum.

As a result of this anomaly, the duodenum frequently becomes irritable and produces the Roentgen signs of a duodenitis. A prolonged stasis was not observed in our cases. The caliber of the duodenum was not enlarged nor was there any evidence of chronic obstruction. No abnormal or exaggerated retroperistalsis was observed in this group.

**Conclusions.** 1. Ten examples of redundant duodenum have been studied and their significance evaluated.

2. The redundant segment occurs most frequently in the superior portion.

3. The redundant duodenum is not an infrequent condition, being more common than is ordinarily recognized.

4. The clinical significance of the redundant duodenum has as yet not been fully established.

5. The coexistence of ulceration with the redundant duodenum is not unusual.

6. The Roentgenologic method of examination offers the best possible means of establishing the diagnosis.

## THE CORRELATION OF OTHER DIAGNOSTIC PROCEDURES WITH CHOLECYSTOGRAPHY IN 250 CASES OF SUSPECTED GALL BLADDER DISEASE.

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THE following analysis of data on 250 recent ambulant and hospitalized patients who, on cholecystographic study, gave evidence of gall bladder disease has been made with two purposes in mind: to test further the reliability of that diagnostic procedure and to determine to what extent other common factors in diagnosis could be correlated with it. No selection of cases has been made except to omit such suspected ones as had negative cholecystograms. This both eliminates the possibility of detecting cholecystographic errors in which disease is present, but is not demonstrable roentgenologically, and fails to give convincing proof of the presence of disease in the cases not operated upon. With these limitations, however, it seems a reasonable approach to the matter of evaluating the significance of the roentgenologic diagnosis of gall bladder disease. At the same time it affords an opportunity to place a relative value on all the diagnostic procedures commonly employed.

The two propositions just outlined were checked by operation in 74 instances (30 per cent). In 176 cases each diagnostic procedure was evaluated in the light of the conclusion reached from the assembled clinical data of the case.

The clinical history, physical examination and cholecystogram now comprise in most clinics an irreducible minimum in the diagnostic study of gall bladder disease not associated with common duct obstruction. In addition to these procedures, which were carried out on all patients of the present series, the following tests were performed in sufficient number to be of statistical value: fractional gastric analysis after a gruel test meal in 184 patients, after histamin in 8, gastrointestinal roentgenography in 117, van den Bergh test in 108 and duodenal drainage by the technique of Jones<sup>1</sup> in 95. An attempt is made to determine the significance in diagnosis of the incidence of other disease along with cholecystitis. Follow-up data on the surgically treated cases are included for the sake of completeness.

The position of the Graham-Cole test as a diagnostic aid is being constantly strengthened by perfection of the technique and by the

publication of comparative figures such as these. In a former paper<sup>2</sup> the limitations of both peroral and intravenous cholecystography as practised in this hospital were summarized and the conclusion reached that in doubtful cases the intravenous method should be used as a check on the routine peroral test.

Recent reports on the effectiveness of special diagnostic tests include cholecystography, but fail to correlate with it all the other commonly used procedures. Bockus<sup>3</sup> expresses the position of those who depend upon duodenal drainage rather than cholecystography for the diagnosis of gall stones. Kirklin,<sup>4</sup> with a wide experience in cholecystography and a progressive attitude toward it, represents those whose reliance is placed very largely in that procedure. Dwyer and Dowling<sup>5</sup> present diagnostic data in regard to history, cholecystography and gastric analysis, in a report dealing particularly with the effects of cholecystectomy. Hoffman<sup>6</sup> studied 155 surgically treated cases to determine the degree of accuracy of certain diagnostic procedures, with emphasis, however, on the clinical data. Fleming,<sup>7</sup> in an appraisal of his experience in 233 proved cases, analyzed the diagnostic reliability of the Graham-Cole test alone.

**Clinical History.** The emphasis to be placed in this review upon cholecystography and other laboratory tests is by no means meant to detract from the value of a well-taken history. The history will be considered first because it emerges, upon analysis of these cases, the most effective single diagnostic item in 126, or half of the series. It remains the chief support in most cases for the clinician's judgment, as Hoffman<sup>6</sup> has recently emphasized. The consistency with which the major symptoms of intermittent right upper abdominal pain and persistent "gaseous indigestion" occur is noteworthy: One or both were present in almost every case. Other items of the history, less frequently found, will be recapitulated because their value was proved in these cases: Familial history of gall tract disease, preceding pregnancies in the patient, adiposity, distress after fatty or "rich" foods, sudden onset of pain, night attacks, nausea and vomiting, necessity for hypodermics and residual local soreness.

In general, we have not attempted to distinguish between gall stones and mere diseased gall bladder wall from the history and physical findings in the absence of jaundice. The contention that distress or pain after eating fatty foods is a differentiating symptom of cholecystitis with stones was not confirmed. In the 64 operatively proved cases distress after fatty food had occurred as a symptom in almost the same proportion of those patients who did not harbor gall stones as those who did, a distinct minority in each class. (Present in 14 cases with stones, absent in 34; present in 4 cases without stones, absent in 12.)

The age incidence of this group of patients is in accord with the

figures commonly accepted. About 80 per cent began to have symptoms between the ages of 20 and 50 years, and the same proportion presented themselves for treatment when they were between 30 and 60 years. Dwyer's figures<sup>5</sup> of 35 per cent below the age of 40 years at admission are duplicated (36 per cent).

TABLE 1.—SEX AND AGE INCIDENCE ON ADMISSION IN 250 CASES OF PROVED OR SUSPECTED GALL BLADDER DISEASE WITH POSITIVE CHOLECYSTOGRAMS.

Sex.	Number.	Per cent.
Females . . . . .	169	68.0
Males . . . . .	81	32.0
Decade		
10 to 19 . . . . .	2	0.8
20 to 29 . . . . .	24	9.7
30 to 39 . . . . .	63	25.0
40 to 49 . . . . .	78	31.2
50 to 59 . . . . .	50	20.0
60 to 69 . . . . .	31	12.5
70 to 79 . . . . .	2	0.8
	250	100.0

TABLE 2.—AGE INCIDENCE IN 235 CASES AT TIME OF ONSET OF SYMPTOMS.

Decade.	Number.	Per cent.
10 to 19 . . . . .	4	1.7
20 to 29 . . . . .	48	20.2
30 to 39 . . . . .	70	30.2
40 to 49 . . . . .	67	28.5
50 to 59 . . . . .	30	12.5
60 to 69 . . . . .	15	6.5
70 to 79 . . . . .	1	0.4
	235	100.0
Uncertain of time of onset . . . . .	15	

The above age incidence figures offer nothing helpful in the differential diagnosis from peptic ulcer, a point which merits reiteration. The age curves both at onset and at admission can almost be superimposed upon those for 221 cases of proved duodenal ulcer reported in 1929 by Miller, Pendergrass and Andrews.<sup>8</sup> The age-at-onset curve likewise approaches closely that of Taylor and Miller<sup>9</sup> for a group of patients with gastric cancer believed to have arisen on an ulcer basis. (Charts I and II.)

The sex incidence figures, however, vary widely for the two groups. In the gall bladder series women predominated 2 to 1; in the ulcer series men outnumbered women 6 to 1. Unfortunately, no anthropometric data as worked out by George Draper are available.

*Physical Examination.* Tenderness in the gall bladder area was present in 70 per cent. The liver was palpated in 19 per cent, the gall bladder itself in only 8 instances (3 per cent). A definite Riedel lobe was described only 3 times in 250 examinations. Muscle resistance was infrequently mentioned, and presumably infrequently determined. There is likewise no indication on the records as to



the extent to which the tests for intercostal neuralgia (Carnett) were applied. Nine per cent of the group showed clinical jaundice at the admission examination.

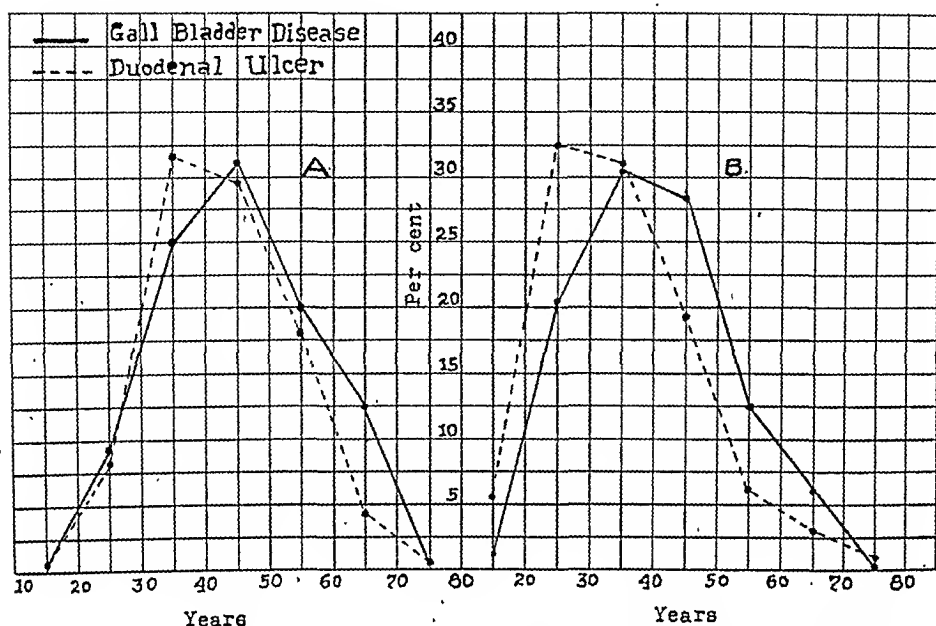


CHART I.—A, age incidence at time of admission to hospital of 250 gall bladder and 221 duodenal ulcer cases. B, age at onset of symptoms in 235 gall bladder and 221 duodenal ulcer cases.

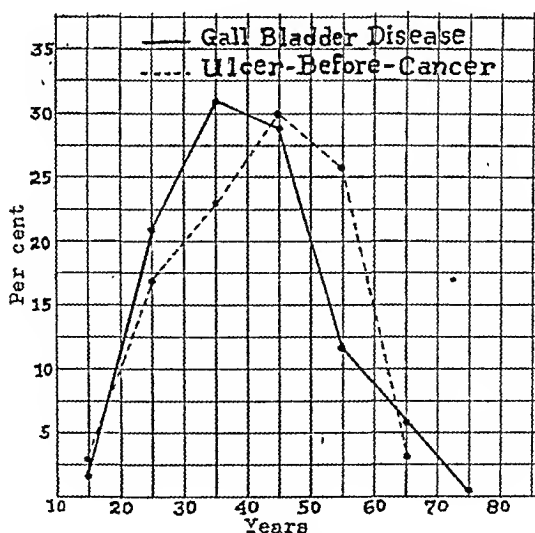


CHART II.—Age at onset of symptoms in 235 gall bladder and 31 gastric ulcer-before-cancer cases.

In summary, the records reveal a tendency to slight the secondary physical signs in these patients, and partly as a result of this the examination outvalued the history and cholecystogram as a factor in diagnosis only 9 times.

TABLE 3.—SYMPTOMS AND SIGNS.

	Number.	Per cent.
Upper abdominal pain . . . . .	214	86.0
Indigestion . . . . .	177	71.0
Jaundice (history) . . . . .	50	20.0
Tenderness in gall bladder area . . . . .	171	69.0
Liver palpable . . . . .	48	19.0
Gall bladder palpable . . . . .	8	3.2
Jaundice (observed) . . . . .	31	12.4

*Cholecystography.* The Graham-Cole test compared most favorably with the history as a trustworthy diagnostic guide. It was found, after all clinical facts were in hand, to be the most valuable diagnostic item in 115 cases (compared to 126 in which the history outvalued it). The test was performed on all patients: 248 patients took the dye by mouth; 56 intravenously, in general as a check on the peroral method.

TABLE 4.—CHOLECYSTOGRAPHY VERSUS CLINICAL HISTORY AND PHYSICAL EXAMINATION.

	Number.	Per cent.
Oral cholecystograms . . . . .	248	99
Intravenous cholecystograms . . . . .	56	22
History most valuable item . . . . .	126	51
Cholecystogram most valuable item . . . . .	115	46
Physical findings most valuable item . . . . .	9	3

Here, as elsewhere, one notices an occasional overstressing of the positive cholecystogram, and tendency to slight the history and other factors in diagnosis. Kirklin<sup>4</sup> and others have stated that the most common source of error in cholecystography is the "normally functioning gall bladder" which nevertheless reveals calculi and inflamed walls to the surgeon. On the other hand, 10 of the 74 cases of this series subjected to operative proof demonstrate again that the roentgenogram of a "poorly functioning gall bladder" occasionally is due to other than gall bladder disease or, indeed, to no adequate cause. These 10 individuals were regarded at operation as having normal gall bladders which were left *in situ*. Their cholecystograms had been made by the peroral technique and were carefully reviewed: All showed the homogeneous opaque substance in the intestinal canal which indicates that absorption of the dye has occurred. In 8 a plausible reason for the absence of shadow lay in abnormality of organs closely associated with the biliary tract (*i. e.*, liver disease, duodenal ulcer, cancer of the pancreas and pyloric stenosis). In this connection Rivers<sup>10</sup> has

stressed the propinquity of duodenum and gall bladder, whereby an inflammatory condition in one organ may alter the function of the other or extend to and involve it to a varying degree. Two of the 8 cases were jaundiced at the time of cholecystography and the error may have been due to this.

In 2 instances, however, operation disclosed a grossly normal biliary system and no disease of adjacent organs. In both the appendix was involved (subsiding acute appendicitis and adherent retrocecal appendix), which may have influenced the cholecystogram in a manner obscure at present. One, therefore, cannot in justice determine the true cholecystographic error in this rather large proportion of disagreement in findings. Furthermore, pathologic examination of the mucosa and walls of these gall bladders might have disclosed disease not evident to the surgeon but sufficient to interfere with function. The above 10 cases are included in the series because, largely due to the cholecystogram, they fell into the group "suspected gall bladder disease," although the pre-operative diagnosis may have been that of other abdominal disorders. They illustrate the danger of the error that lies in over-much dependence on a single test, no matter how efficient.

TABLE 5.—OPERATIVE FINDINGS IN THE 74 OF 250 CASES WITH POSITIVE CHOLECYSTOGRAMS THAT CAME TO LAPAROTOMY.

Gall bladder disease . . . . .	64
Gall bladder normal, other abdominal lesions . . . . .	10
Cirrhosis of liver . . . . .	2
Duodenal ulcer . . . . .	2
Carcinoma of pancreas with jaundice . . . . .	1
Pyloric stenosis . . . . .	1
Narrow common duct, with pyloric stenosis . . . . .	1
Spastic duodenum, excess motility . . . . .	1
Appendicitis . . . . .	2

*Gastrointestinal Roentgenography.* We have made roentgenologic study of the stomach and intestine with the opaque meal in 47 per cent of the present series. Although detailed studies of the relationship of the alimentary tract to the abnormal gall bladder were not made, it is significant that the duodenum was deformed by adhesions in 53 per cent of the 117 cases. Among 30 proved cases 60 per cent showed such duodenal deformity. Duodenal stasis occurred in 10 per cent, while in only 24 per cent of the total was the upper gastrointestinal tract normal roentgenologically.

The procedure is indicated in obscure cases, in our opinion. The helpful diagnostic evidence to be obtained from such study is seemingly not appreciated in many American clinics, so that Rossi of the University of Parma, in describing the valuable features of his combined cholecystographic and gastrointestinal technique,<sup>11</sup> can with some justice write: "Almost always, especially abroad, there has been omitted an accurate study of the gastrointestinal tract." He gives the patient an opaque, fatty paste instead of the

fatty meal, and studies serially the shape, position and functional activity of the stomach and intestine while the gall bladder is contracting. Levene and Whitaker,<sup>12</sup> in 1930, reported good results from the simultaneous observation of stomach, duodenum and gall bladder action. Nevertheless, possibly due to the rather exacting and time-consuming technique, the combined method has not gained wide acceptance in this country.

TABLE 6.—GASTROINTESTINAL ROENTGENOGRAPHIC FINDINGS.

	In 117 patients with positive cholecystograms.		In 30 cases of diseased gall bladder at operation.	
	Number.	Per cent.	Number.	Per cent.
Deformed duodenum (adhesions)	62	53	18	60
Normal	29	24	5	17
Upper intestinal stasis	11	10	2	7
Pylorospasm or deformed pylorus	7	6	3	10
Duodenal ulcer	6	5		
Gastric polyp	1	1	1	3
Excess motility	1	1	1	3

*Duodenal Drainage.* This procedure has been in use in our Gastrointestinal Section since 1927. The early results on a small group of patients were reported in 1929.<sup>13</sup> Throughout, the technique advocated by Jones<sup>1</sup> has been followed with the following results in 95 cases (31 per cent): Half of the examinations offered confirmatory evidence of cholecystic disease; the other half gave results which were not helpful, in that the findings in the centrifuged sediment were entirely negative, when other evidence pointed to disease, or when in the absence of definite crystals the examiner could not be certain that the formed elements seen denoted true biliary pathology. Approximately the same results appeared in 30 cases subsequently proved.

TABLE 7.—DUODENAL DRAINAGE IN 95 GALL BLADDER SUSPECTS.

	Number.	Per cent.
Of diagnostic value . . . . .	46	48
(Crystals, 33)		
Doubtful value . . . . .	25	26
(Negative, pus cells, epithelium)		
No value . . . . .	24	26
(Disagrees with final diagnosis or operative findings)		

TABLE 8.—DUODENAL DRAINAGE IN 30 CASES OF PROVED BILIARY DISEASE.

	Number.	Per cent.
Crystals . . . . .	12 (stones, 10)	41
Excess pus cells . . . . .	5 { gall bladder ulcerating, 2 } { stones, 2 }	16
Negative . . . . .	10 { no stones, 6 } { stones, 4 }	33
Doubtful . . . . .	2	6
Unsatisfactory . . . . .	1	3

The negative drainages in positive cases, which have formed the bulk of the unsatisfactory tests to date, have, in our present

more complete knowledge of the method, been due in large part to two factors: The impossibility, until recently, in the Section or the wards of assigning the conduct of the test to a single thoroughly trained member of the staff, and an insufficient number of diagnostic drainages in the doubtful cases. Those who have reported great success with the test<sup>3</sup> emphasize these points. Our results have demonstrated that to be of consistent value, every step of the technique must be presided over by an expert. Provided the conditions are fulfilled, there is no doubt that the failure to obtain brown gall bladder bile or the finding of cholesterol or calcium bilirubin crystals or large numbers of deeply bile-stained pus or columnar cells is evidence of gall bladder disease.

*Gastric Acidity.* Analyses of the gastric contents were made with the gruel test meal in 184 of the entire group and 53 of the proved cases. The histamin test was made 31 times, in 23 instances after the gruel meal had developed little or no free acid. Of the 23 patients, 17 showed adequate acid figures under the increased stimulus. However, because of the great variability of response to histamin, precluding any "normal" standard, and because the histamin series is quite small, it is not deemed worthwhile to include it in the tabulation. Histamin is used at present in the Section only to distinguish true from false achlorhydria.

The results of the gruel meal are likewise hard to standardize and comparison with the figures in other published reports is almost worthless because of the great variation that prevails in the type of meal used and the technique of collection. However, setting the limits of 10 to 40 (cc.  $\frac{N}{10}$  HCl per 100 cc.) for normal range of free acid response in the 90-minute fractional test, with gruel, the incidence of hypochlorhydria and achlorhydria in the general and the proven groups was 38 and 31 per cent, respectively. This is a distinctly higher proportion than obtains for the patients of the Section as a whole. The patients showing excess acid secretion were in small number, 10 and 4 per cent, respectively.

TABLE 9.—GASTRIC CONTENTS (FRACTIONAL ANALYSIS, GRUEL MEAL).

	In 184 patients with positive cholecystograms.		In 53 operatively proved cases.	
	Number.	Per cent.	Number.	Per cent.
Normal . . . . .	96	52	34	65
Hypochlorhydria . . . . .	43	23	7	12
Achlorhydria . . . . .	28	15	9	19
Hyperchlorhydria . . . . .	17	10	3	4

With 2 exceptions to be mentioned, the hyperchlorhydria patients gave the histories of short duration and the patients with depressed acid as a rule the longer ones. The average duration of symptoms in the high acid group including 1 12- and 1 15-year history was 3.6 years. The average for the same hyperchlorhydria patients, with these 2 histories omitted, was 2.4 years. In comparison, the

average duration for the low acid cases was 4 years, and for the normal acid cases 3.1 years.

One is justified, probably, from these results, in saying that evidence is hereby added that hypochlorhydria and achlorhydria are more common in gall bladder disease than in normal persons and gastrointestinal patients other than those with gastritis or malignancy. Furthermore, the incidence of hyperacidity is relatively small, and the condition is found, by and large, early in the disease. The discovery of depressed or absent free hydrochloric acid may thus be of use, with an extended history of indigestion, as a link in the chain of diagnostic facts denoting gall bladder pathology.

*Van den Bergh Test.* In the presence of clinical jaundice the van den Bergh test, repeated every few days, is of value in determining whether any regression of the jaundice is occurring. Its chief value, however, lies in the ability of the indirect reaction, with the icterus index, to pick up latent jaundice, not detectable otherwise. In the doubtful case such indication of liver or biliary tract abnormality may clinch the diagnosis. The test was performed 1 or more times on 108 individuals. It demonstrated latent jaundice, not detectable clinically, in 22 per cent; among the proved cases in 29 per cent. The test is worthy of retention in gall bladder diagnosis, indeed of more frequent application than was made in the present series.

TABLE 10.—VAN DEN BERGH TEST.

	In 108 patients with positive cholecystograms.		In 24 operatively proved cases.	
	Number.	Per cent.	Number.	Per cent.
Negative . . . . .	56	52	9	38
Direct positive (jaundice) . . . . .	29	27	8	33
Indirect alone positive (latent jaundice) . . . . .	23	21	7	29

TABLE 11.—VERIFIED COMPLICATING LESIONS IN 250 CASES.

Heart disease:		Duodenitis . . . . .	1
Myocardial (with symptoms) . . . . .	13	Carcinoma, primary, in duo-	
Chronic valvular . . . . .	2	denal wall . . . . .	1
Appendicitis:		Gastric polyp . . . . .	1
Acute . . . . .	1	Diabetes mellitus . . . . .	4
Chronic . . . . .	6	Hypertension . . . . .	4
Liver disease:		Syphilis . . . . .	2
Hepatitis . . . . .	6	Renal calculus . . . . .	1
Catarrhal cholangitis . . . . .	2	Pyelonephritis . . . . .	1
Carcinoma (primary) . . . . .	1	Toxic goiter . . . . .	1
Duodenum:		Colitis . . . . .	1
Ulcer . . . . .	3		
Diverticulum . . . . .	1		52

*Complicating Diseases.* This group of cases is too small to offer evidence of value in determining the diseases most likely to be associated with cholecystitis. It does, however, bear out the impression widely held, and recently put in tabular form by Rivers and Hartman,<sup>10</sup> of the high proportion of coincident disease. The

proved coexisting lesions among these 250 individuals were divided among 13 disease groups, and occurred in more than one-fifth of the cases (21 per cent). Myocardial disease with symptoms was perhaps more frequent here (5 per cent) than among the population at large of similar age range.

*Follow-up.* The figures of the results of surgical treatment, included by courtesy of Drs. Müller and Eliason, on whose services the patients underwent operation, are included simply to indicate the type of result to be expected from conservative surgery in contrast to the known poor result of any medical therapy.

TABLE 12.—FOLLOW-UP, 4 MONTHS TO 3 YEARS, ON 50 PATIENTS WITH OPERATIVELY PROVED GALL BLADDER DISEASE.

	Well.	Improved.	Unimproved.	Died.
Cholecystectomies, 43.				
Cholecystitis . . . . .	3	1	1	2
Stones in gall bladder . . . . .	21	7	2	0
Stones in common duct . . . . .	2	0	2	2
	<hr/>	<hr/>	<hr/>	<hr/>
Totals . . . . .	26	8	5	4
Cholecystostomies, 7.				
Cholecystitis . . . . .	0	2	0	0
Stones in gall bladder . . . . .	3	2	0	0
	<hr/>	<hr/>	<hr/>	<hr/>
Totals . . . . .	3	4	0	0

**Conclusions.** 1. The diagnostic procedures in gall bladder disease which have proved of most value in this clinic are, in order of their effectiveness in 250 instances: (1) A careful and complete history and physical examination; (2) cholecystogram; (3) gastrointestinal roentgenography; (4) duodenal drainage; (5) the van den Bergh test and icterus index; (6) fractional gastric analysis.

2. Gastrointestinal roentgenography can be made of more positive value in diagnosis of cholecytic disease than is the case at present.

3. Duodenal drainage can be made effective in diagnosis by very careful routine technique and examinations to be made only by a thoroughly trained person, preferably a physician. Otherwise the procedure is not worth the time and effort involved.

4. While each one of these procedures will not be needed in every instance of suspected biliary disease, together, if carefully done, they are adequate to give in the doubtful case sufficient data to warrant decision for or against laparotomy.

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## THE PERSONALITY TYPE OF PATIENTS WITH ARTERIOLAR ESSENTIAL HYPERTENSION.

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It has long been believed that patients with arteriolar essential hypertension have special physical and emotional reactions to life—in other words, that such patients have a special type of personality. If this is true, then the knowledge and application of this fact may not only aid the diagnosis and therapy of this disease, but may afford insight into its etiology. Unfortunately, the evidence for this idea of a special hypertensive type consists almost wholly of clinical impressions. It has been the purpose of the present investigation to test the validity of these clinical impressions by controlled study.

**Literature.** In accord with many writers on this aspect of the subject, Mosenthal<sup>1</sup> states that arteriolar (essential) hypertension "occurs rather more frequently in the highstrung, nervous, or irritable individual." Likewise O'Hare<sup>2</sup> says that "almost all have been of a nervous temperament throughout life." Herriek<sup>3</sup> believes that hypertensive patients have an "ill-balanced personality" whose chief tendencies are "pressure of activity and over-earnestness." He says further that they are "serious, earnest, conscientious, enthusiastic at work, at their infrequent play, and too often at table." Barach<sup>4</sup> finds that early in life hypertensive patients have "a certain instability, restlessness, a lack of confidence and shirking of responsibility . . . During middle life . . . they frequently are restless or ineffectual, or they may be abnormally active and intensive in their special field of endeavor." Mosecowitz<sup>5</sup> has presented one of the most detailed and interesting descriptions of the hypertensive type. He has observed among other things that "the greatest proportion of patients with hypertension are terribly tense and pursue their vocation with tremendous seriousness, and



worry over trivialities. In consequence, they are irritable. They are the antithesis of the child. They do not play. They have no time for play. They have narrow intellectual horizons." In general, the above writers believe that hypertensive patients tend to be highstrung, serious, and overactive.

Several physicians have tried to verify these valuable clinical impressions by more exact studies. O'Hare, Walker and Vickers<sup>6</sup> analyzed the records of 300 hypertensive patients whose average age was 51 years. They found that 42 per cent had one or more of the following symptoms in their early history: "Frequent epistaxis; abnormal flowing at menstruation; migraine; cold, sweaty, and cyanotic hands; flushing; blushing; extreme sensitiveness; a highstrung and nervous temperament, etc. In 100 of these hypertensive patients who were questioned especially for these symptoms, we were able to establish their presence in 87 per cent." By contrast, in 436 patients with normal blood pressures whose average age was 36 years, these "symptoms of vasomotor weakness, etc., were noted in only 23 per cent" of the records analyzed. On the other hand, the studies of Patek and Weiss<sup>7</sup> showed no striking differences in personality between a group of 47 hypertensive patients and 37 patients with normal blood pressure. On questioning their patients they found that 67 per cent of the hypertensive patients were "excitable" as compared with 54 per cent of the control group; 75 per cent of the hypertensive patients were "hyperactive" as compared with 65 per cent of the control group; 53 per cent of the hypertensive patients were "impulsive" as compared with 37 per cent of the control group; and 83 per cent of the hypertensive patients "worried excessively" as compared with 54 per cent of the control group. Thus, the only definite "difference between the two groups was in their relative propensities to worry."

Neither of these studies offers adequate proof for or against the existence of a special hypertensive personality. O'Hare, Walker and Vickers studied the psychic and vasomotor reactions of only the early life of hypertensive patients, without inquiring into the reactions of these patients during their later years. Furthermore, the average age of the control group was 15 years less than the average age of the hypertensive group so that many in this younger control group might develop hypertension in the following 15 years. In the study of Patek and Weiss, no mention is made of the age of their patients other than that both groups had "similar age distribution." Most important, they do not state the method of questioning their patients or the questions asked. This information is essential in evaluating their results. It is easy to obtain affirmative answers from the majority of people who are asked, for example, "Are you sensitive?"; a much smaller number will respond in the affirmative to the question "Are you unusually sensitive?"; while a still smaller number will give positive answers to the question, "In

general, have you been more sensitive than the average person?" In neither of the above studies was mention made as to what was considered normal blood pressure. Both of the studies were carried out on ward patients and, therefore, many of the normal patients may easily have had mild hypertension which dropped to normal during bed rest or during inactive ward life.<sup>8</sup> Furthermore, in both of the studies, the control cases were sick ward patients. Therefore, these control patients were not healthy normal people, but sick patients with normal blood pressure. The above studies really constitute a comparison of the personality type of hypertensive patients with the personality types of patients with peptic ulcer, bronchial asthma, tuberculosis, carcinoma, etc., who had normal blood pressure. Diseases like peptic ulcer, for example, may possibly occur in people of certain personality types,<sup>9</sup> so that the personalities in the control groups of the above studies are not those of a truly normal group of people. The literature, therefore, indicates the need of further study of the personality in hypertensive patients.

**Clinical Material of Present Study.** The clinical material used in the present study consisted of 182 ambulatory "patients" seen in dispensary and private practice. The details of age, sex, weight, blood pressure, etc., of these patients are presented in Table 1. The standards of normal blood pressure used in this study are those of Rogers and Hunter.<sup>11</sup> The subjects fall into the following 5 clinical groups:

TABLE 1.—CLINICAL MATERIAL OF PRESENT STUDY.

Groups.	Number of patients.	Number of females.	Average age of group, yrs.	Range in age.	Range of systolic blood pressure, mm. of Hg.	Range of diastolic blood pressure, mm. of Hg.	Average weight of group above normal standard for age and height, in pounds.*
1 . .	41	28	54	36 to 74	160 to 280	90 to 160	14.7
1a . .	20	11	56	39 to 67	160 to 260	92 to 158	7.0
2 . .	34	12	26	15 to 35	150 or more in 50% 140 or more in 80%	90 or more in 33%	11.3
3 . .	35	12	47	36 to 71	130 or less in 75% 130 to 140 in 25%	less than 90 in 86% 90 to 100 in 14%	8.0
4 . .	52	17	25	15 to 35	130 or less in all 124 or less in 70%	80 or less in all 70 or less in 50%	5.5

\* See No. 10 in bibliography.

*Group 1.* Middle-aged hypertensive patients with symptoms.

*Group 1a.* Middle-aged, symptom-free, hypertensive patients. Most of the patients in Groups 1 and 1a had secondary cardiac enlargement and retinal vascular changes, while a few had mild secondary renal damage.

*Group 2.* Young hypertensive individuals. Twenty-one of the patients in this group made two or more visits, and 50 per cent of those seen on a second visit still had abnormally high systolic pressures. Only 2 patients continued to have abnormally high diastolic blood pressures at the second visit. Twenty-five of the subjects in Group 2 were children of parents with definite essential hypertension, were symptomless, and had not requested medical attention. The parents had been examined by the author.

*Group 3.* Middle-aged control subjects with normal blood pressure. Most of the patients in this group were either healthy people who wished a general examination, or ambulatory people referred for general medical examinations because of uncomplicated gonorrhea, obesity, skin diseases, primary syphilis or varicose veins. All of these patients had few if any symptoms.

*Group 4.* Young control subjects with normal blood pressure. Twenty-seven of the 52 patients were referred for general medical examinations because of uncomplicated gonorrhea or skin diseases. They had few, if any, symptoms. The remaining 25 subjects were children of parents with definite essential hypertension, were symptomless, and had not requested medical attention. Their parents had been examined by the author.

**Method of Present Study.** The same specifically worded direct questions in regard to personality were asked of the control subjects and the patients with hypertension. There was no hesitancy by the author of employing direct questions because both control and hypertensive subjects were subjected to the same method of questioning. This method of allowing the subject to evaluate his own personality is considered very satisfactory when dealing with nonpsychotic individuals who have no reason to conceal anything. Only subjects who readily grasped the questions were utilized. It was a striking fact that the great majority of people were able to give a prompt reply to the questions asked. It might be argued that hypertensive patients may possibly be more introspective than subjects with normal blood pressure. This possible error was found to be absent, for, on inquiring in many cases among the intimate relatives of the subjects, the relatives agreed that the subjects evaluated their personality quite accurately. Each subject was questioned in such a way as to avoid as far as possible being influenced by the tone of the questioner. In about 20 per cent of the subjects the personality study was made before the blood pressure reading was determined. The questions selected referred partly to personality characteristics commonly mentioned in the literature as associated with hypertension, and partly to personality traits with which I personally have been impressed in hypertensive patients.<sup>12</sup> The entire study, including determinations of the blood pressure, was carried out by the author. The blood pressure was determined by the mercury sphygmomanometer and auscultation. The end of the third phase was the criterion of diastolic blood pressure. The complete list of the questions as they were asked is as follows:

1. In general, throughout your life, not on any one special occasion, and compared to the average person of your own age with whom you have come in contact, have you been of an unusually highstrung nature or of a calm nature?

2. In general, throughout your life, not on any one special occasion, and compared to the average person of your own age with whom you have come in contact, have you been the sort of person who loses his temper quickly (who flies off the handle easily over little things) or has it usually required a good deal to make you lose your temper?

3. In general, throughout your life, not on any one special occasion, etc. . . . (as in Question 2) . . . have you been the sort of person who even if you don't show it externally, feel yourself frequently getting all excited over little things?

4. In general, etc. . . . (as in above questions) . . . have you been the sort of person whose feelings are unusually easily hurt, who is unusually sensitive, or does it take a great deal to make you feel hurt?

5. As a younger person did you or do you still blush or flush unusually easily compared to the average person your age? Would people "kid you about it?"

6. As a younger person, did you or do you still become unusually easily embarrassed compared to the average person?

7. In general, etc. . . . have you been the sort of person who worries unusually easily over little things, or have you tended to pass them over?

8. In general, etc. . . . (as in Questions 1 and 2) . . . have you been of an unusually serious nature or of a happy-go-lucky nature?

9. In general, etc. . . . have you been of an unusually forward or unusually shy nature?

10. In general, etc. . . . have you ever had frequent nosebleeds?

11. In general, etc. . . . have your hands or feet tended to become easily cold on slight changes in weather?

12. In general, etc. . . . have you tended to walk at an average pace, slower than the average person, or faster than the average person?

13. In general, etc. . . . have you tended to work at an average pace, slower than the average person, or definitely faster than the average person?

14. In general, etc. . . . have you tended to eat or talk at an average rate, slower than the average person with whom you eat (or talk) or faster than the average person.

15. In general, etc. . . . have you been of average, less than average, or more than average physical activity?

Only definite replies were used, so that when a patient stated that he could not definitely answer, that particular patient was not credited with any reply to that special question. Where the patient stated that a particular trait had existed in him for only a few years rather than his whole life, he was credited as not having that trait throughout his life, that is, from the point of view of the present study, that trait was absent most of his life.

**Results.** The results of the questioning are presented in Tables 2 and 3. Let us temporarily omit a consideration of the selected Group 1a. It is seen that 52 per cent of both the older and the younger hypertensive persons (Groups 1 and 2) stated that they were unusually highstrung their whole life, compared to only 3 and 6 per cent of the corresponding control groups (3 and 4). Of the older group, 43 per cent, and of the younger, 53 per cent stated that they were unusually quick tempered their whole life, compared to only 3 and 13 per cent for the replies of the corresponding control groups. Of the older group, 69 per cent, and of the younger, 66 per cent said that they were unusually sensitive their whole life, compared to 9 and 18 per cent for the replies of the corresponding control groups. Of the older group, 70 per cent, and of the younger, 58 per cent said they worried unusually easily over little things their whole life, compared to only 11 per cent of the corresponding control groups. Of the older patients, 94 per cent, and of the younger, 69 per cent said that, compared to the average person their own age, they were definitely more active physically their whole life, compared to 13 and 10 per cent for the answers of the corresponding control groups. This unquestionable preponderance of high percentages among the hypertensive groups is seen also in the answers to practically all the other questions (Table 2).

Referring to Table 3 it is seen that the frequency of the various

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traits in the hypertensive patients becomes exceedingly high when the replies to two or more questions are added together. Thus, for example, 97 per cent of the older and 70 per cent of the younger hypertensive patients said they were either unusually highstrung, or unusually active, or both, compared to 7 and 15 per cent for the replies of the corresponding control groups. This was one of the outstanding correlations of the entire study. Further correlation of combined questions are seen in Table 3.

TABLE 2.—PERCENTAGE INCIDENCE OF CERTAIN PERSONALITY CHARACTERISTICS IN SUBJECTS WITH HYPERTENSION AND WITH NORMAL BLOOD PRESSURE.

Group No.	Blood pressure.	Average age.	Number of patients.	Unusually highstrung.	Unusually quicktempered.	Unusually easily excited within themselves.	Unusually sensitive.	Unusually easy blushing.	Unusually easy embarrassment.	Unusually easy worrier.	Unusually serious.	Unusually shy.	Unusually fast walker.	Unusually fast worker.	Unusually fast talker or eater.	Unusually active physically.	Frequent epistaxis.	Hands or feet easily cold.	Family history of vascular disease.
1.	H*	54	41	52	43	54	69	65	48	70	59	70	58	87	64	94	2	13	71
1a.	H	56	20	30	25	25	35	35	30	50	..	60	65	50	70	..	..	..	..
2.	H	26	31	52	53	64	66	38	44	58	61	58	70	68	69	6	17	77	..
3.	N	47	35	3	3	6	9	21	23	11	19	44	29	33	28	13	6	11	25
4.	N	25	52	6	13	12	18	25	11	11	23	21	20	29	24	10	0	20	62

\* Abbreviations in all the tables are the same. H = hypertension. N = normal.

TABLE 3.—PERCENTAGE INCIDENCE OF CERTAIN PERSONALITY CHARACTERISTICS IN SUBJECTS WITH HYPERTENSION AND WITH NORMAL BLOOD PRESSURE.\*

Group No.	Average age.	Number of patients.	Unusually highstrung or quicktempered, or easily excited within themselves.	Unusually quicktempered or sensitive.	Unusually serious or sensitive.	Unusually sensitive or quick worker.	Unusually quicktempered or quick worker.	Unusually highstrung or active.	Unusually easy blushing or shyneess.	Unusually quicktempered, or sensitive, or serious or active.
1	54	28	68	77	85	93	94	97	90	90
1a	56	20	50	40	60	80	70	75	..	80
2	26	28	76	74	81	90	80	76	70	..
3	47	31	3	9	25	36	30	7	39	35
4	25	46	12	29	35	41	36	15	33	..

\* Figures obtained by adding together the positive replies to two or more questions.

Turning next to Group 1a in Table 2, consisting of the specially selected, symptomless hypertensive subjects, it is first seen that to

every question there was also a definitely higher percentage of positive answers than in both control groups. However, compared to the other hypertensive groups (1 and 2), Group 1a had a much lower number of positive answers to the questions dealing with the emotional responses such as quick temper and sensitiveness. On the other hand, to the questions relating to physical activity, the symptomless hypertensive patients gave almost as high a percentage of positive answers as the other hypertensive groups.

**Discussion.** The present study confirms the often mentioned clinical impression that persons with arteriolar (essential) hypertension tend to have certain emotional and physical reactions much more frequently and intensely than comparatively healthy people of the same age group and with normal blood pressure—in the present study from 2 to 17 times as commonly as do the normal controls (Tables 2 and 3). The results confirm the author's previous impressions that hypertensive patients tend to be emotionally hyperactive, physically hyperactive, or both. In presenting and discussing the statistical data in Tables 2 and 3, the author has had only one purpose—to indicate trends rather than immutable statistics. Thus, the results in Tables 2 and 3 indicate that hypertensive patients tend to be highstrung individuals who either display quick temper or are easily excited within themselves. They tend to be unusually sensitive, being hurt by little things. In youth and often persisting to later life, they tend to blush easily, to be easily embarrassed, and to be unusually shy. In dealing with the events of life, however minute, they tend to be unusually serious and worry over trivialities. However, as seen in Table 2, a much smaller percentage of the symptomless hypertensive patients admit that they are emotionally hyperactive, although this percentage is definitely greater than in the control group. Physically, whether symptomless or not, the hypertensive individual seems to be an unusually rapid walker, even when in no special hurry. Hypertensive subjects tend to work at their tasks in home or in office with much more rapidity and thoroughness than the average person. They often tend to eat or talk rapidly. In general, they tend to be unusually active physically, in their domestic, occupational, and social activities. It cannot be too strongly emphasized that the author does not believe that every person with a hypertensive type of personality has or will develop arteriolar (essential) hypertension. Neither is it meant that every hypertensive patient has the type of personality above presented. It is clear, however, that most hypertensive patients in the groups studied are of the personality type described.

**The Hypertensive Personality is of Lifelong Duration.** Not only does the middle-aged hypertensive patient tend to be of a certain personality type, but the replies indicate that so far as he can remember he has always been of that type. It seems likely, there-

fore, that the hypertensive personality is present and recognizable in early life. This likelihood is further confirmed by the study of the younger hypertensive group, which already at an average age of 26 shows exactly the same type of personality reactions to life as the older group. The probability that most of the persons in our younger group with abnormally high blood pressure readings are cases of early arteriolar (essential) hypertension, is enhanced not only by the finding in them of a similar type of personality as in the older hypertensive patients, but also by the significant fact that about 80 per cent of them are the children of known hypertensive patients.

**Differentiating the Hypertensive Personality from Other Types.** It is important to distinguish the hypertensive personality from that present in anxiety-neurosis with normal blood pressure and in the manic-depressive type of individual. Thus, it is well known that hyperactive emotional responses are present in many nonhypertensive people who undergo marked emotional strain. In such people the emotional strain may cause not only hyperactive emotional responses, but also bodily symptoms—in other words the picture of the psychoneuroses. However, the difference between the hyperactive emotional responses of the hypertensive patients and of the psychoneurotic patients is usually one of duration—the personality type of the hypertensive person being lifelong, whereas in most psychoneurotics it is only as long as the existence of the emotional upset.<sup>13</sup> Yet there are many psychoneurotic patients of almost lifelong duration. It is obvious, therefore, that a study such as this must try to avoid the use of subjects who have symptoms of psychoneuroses, or take account of it.

Therefore, as a control for this factor the personality of a group of symptom-free hypertensive individuals was studied. This group of 20 persons gave no history of symptoms suggesting psychoneurosis. They prided themselves on being unusually well all their lives and of practically never going to doctors. If it is true that many of the symptoms of hypertensive patients are due to emotional disturbances,<sup>13</sup> it would seem likely that symptom-free hypertensive "patients" should have a less frequent incidence of traits associated with emotional instability than hypertensive patients with symptoms. This is exactly what was found in Group 1a. In these 20 symptomless hypertensive patients, only 30 per cent stated they were unusually highstrung compared to 52 per cent in the hypertensive patients with symptoms; 25 per cent said they were unusually quick-tempered, easily excited, or unusually sensitive, compared to 53, 64 and 66 per cent respectively in the symptom group. However, the hyperactive physical responses in the symptom-free group were as frequent as in the other hypertensive groups studied.

The hypertensive personality is quite different from that of the

neurasthenic individual. The latter, as a rule, may be emotionally hyperactive for a period, but is not physically hyperactive. He fatigues easily—one of the outstanding characteristics of the neurasthenic. He may want to do a great deal, but is unable to do so physically, which is in direct contradistinction to the hypertensive type.

The hypertensive personality must be distinguished also from the manic-depressive type. There are many people who will say that they are of the hypertensive type but have no hypertension. Many of these people, however, are of a manic-depressive type of personality without being psychotic. They have a great deal of physical energy and enthusiasm, but it is not a constant thing. Akin to the actual manic-depressive psychoses, they have periods in which they are unusually energetic, often lasting for months or more, followed by periods of depression during which their activity is much less. The hypertensive patient, however, has a drive within him which is persistent, steady, and not broken up by periods of depression. However, one cannot be dogmatic; for, mixed types often occur, and a hypertensive patient may have a depression.

**Etiology of the Hypertensive Personality.** This matter is unsettled. Moschcowitz<sup>5</sup> believes it may be of environmental acquired origin, "the result of imitative tendency of children," which gives a pseudo-hereditary aspect to it. Against the environmental etiology of the hypertensive personality are 25 of the young control individuals in Group 4, who, although they are the children of hypertensive patients and they have lived in the environment of these parents and of their hypertensive brothers and sisters, have neither the hypertensive personality nor elevated blood pressure like their brothers and sisters. Barach,<sup>4</sup> on the other hand, believes the hypertensive personality is primarily the result of physical influences, like the personality changes in myxedema, hyperthyroidism, or eunuchoidism. It is highly possible that the hypertensive personality is of physical, perhaps endocrine origin. Certain it must be, in the light of the present study, that the hypertensive personality, present as it is early in life, can be neither the result of any unusually high blood pressure, nor the result of secondary vascular disease. It is also unlikely that it is due to environmental imitation of parents.

**Relation of the Hypertensive Personality to the Diagnosis of Essential Hypertension.** The recognition of the hypertensive personality may be of definite aid in the diagnosis of arteriolar (essential) hypertension. Given a patient in whom the diagnosis of chronic vascular nephritis secondary to arteriolar hypertension is difficult to separate from a diagnosis of chronic glomerular nephritis with hypertension, the absence of the hypertensive personality is one more bit of evidence in favor of the primary kidney disease, rather than the hypertensive origin. The hypertensive personality type may also be of



aid in the diagnosis of early arteriolar hypertension; for, given a young person with mild fluctuating hypertension, the presence of the hypertensive personality, especially in the presence of a positive family history of vascular disease, strongly supports the diagnosis of early arteriolar essential hypertension rather than simple emotional hypertension. I believe that it is here that the knowledge of the hypertensive personality has one of its greatest applications—the early diagnosis of this disease. One may go even still further and say, as O'Hare<sup>14</sup> has, that the presence of vasomotor instability (and I would add the hypertensive type of personality) in children of a hypertensive patient, even before the existence of hypertension, calls for prophylactic measures.

**The Hypertensive Personality in Treatment of Arteriolar Essential Hypertension.** Elsewhere I have described<sup>12</sup> the importance of attempting to modify the hypertensive personality in the treatment of arteriolar essential hypertension. The relation of the hypertensive personality to the production of early symptoms has already been discussed,<sup>13</sup> so that therapy of early symptoms must take account of this fact. Suffice it here to say, that it is well known that the hyperactive emotional and physical responses of the hypertensive patient are accompanied by marked elevations in blood pressure. Therefore, any rational therapy of arteriolar essential hypertension must attempt to modify this personality, either by education, sedatives, or both.

Finally, it is sincerely hoped that the present study will stimulate further investigation of the hypertensive personality by specially trained students of personality.

**Summary and Conclusions.** 1. A simple study of the personality of 182 subjects has been made. These subjects consisted of middle-aged hypertensive patients, hypertensive patients between the ages of 18 to 35, middle-aged normal subjects with normal blood pressure, and young normal subjects with normal blood pressure.

2. The results indicate that hypertensive subjects tend to have a distinct type of personality. Their personality is characterized by increased psychomotor activity. They are dynamic, hyperactive individuals, with a large and steady output of energy. They tend to be sensitive and quick-tempered. The mood fluctuations, however, are not an important feature, which differentiates them from the manic-depressive individuals. The hypertensive personality has existed as far back as the subject can remember.

3. The relation of the hypertensive personality to the diagnosis and treatment of arteriolar essential hypertension is discussed.

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## THE FRACTIONAL PHENOLSULPHONEPHTHALEIN TEST IN BRIGHT'S DISEASE.

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SINCE the introduction of the phenolsulphonepht halein test of kidney function by Rowntree and Geraghty<sup>9</sup> the method commonly used has been the estimation of the dye excreted in specimens of urine collected 1 and 2 hours after injection. The value of this test in severe nephritis has been generally recognized. However, Christian and O'Hare<sup>3</sup> and others have observed that this test fails to reflect the impaired function in moderate or slight degrees of nephritis, and they place more reliance on the 2-hour concentration test. In cases of mild or suspected nephritis Bowen<sup>2</sup> found the phenolsulphonepht halein test less informative than tests of urea excretion. Van Slyke, McIntosh, *et al.*<sup>13</sup> have recently concluded that the urea clearance test shows diminution of renal function before the phenolsulphonepht halein test.

Rowntree, in 1910, stated that the "curve of elimination of phenolsulphonepht halein in nephritis differs from the normal in that the maximum intensity is slowly reached." Later Snowden<sup>12</sup> noted that the earliest indication of impaired renal function was a delay in the excretion of dye. Thus a patient with Bright's disease may have a total output of 60 per cent in 2 hours with only 30 per cent appearing in the first hour, whereas in the normal person 50 per cent appears in the first hour. In 1925 Shaw<sup>11</sup> determined the

normal curve of dye elimination by collecting urine at 5- and 15-minute intervals after intravenous injection and found that an average of 40 per cent of the dye appeared in the first 15 minutes. He applied this technique of fractional collections to cases of renal disease and found marked abnormalities in the curve of excretion in many cases where the 2-hour output was normal. A decreased output in the first 15 minutes or a delay in the peak of elimination was frequently the only evidence of kidney disease.

It is surprising that this important modification has had clinical application, to our knowledge, only in urologic surgery. We have employed Shaw's method of frequent collections, which we have called the *fractional phenolsulphonephthalein test*, in order to determine whether or not it gives a better indication of kidney function in Bright's disease than the usual method of hourly collections, and also to determine its comparative value with the urea clearance test.

**The Excretion of Phenolsulphonephthalein in Normal Individuals.** Chart 1, Fig. 1, indicates the variations of the curve of phenolsulphonephthalein excretion which we have obtained from 40 tests on 20 normal individuals ranging in age from 11 to 40 years. Two tests were done on each at an interval of several days. The subject voided, drank 600 cc. of water and after 30 minutes 1 cc. (6 mg.) of phenolsulphonephthalein was injected intravenously. Voided specimens of urine were then collected at intervals of 15, 30, 45, 60 and 120 minutes. Estimations of the per cent of dye excreted were made with a Duboscq colorimeter, using standards freshly prepared with phenolsulphonephthalein.

Except for the slightly lower average 15-minute output, this curve (Fig. 1) is similar to that described by Shaw. Seven initial readings were above 40 per cent and 3 were below 30 per cent. Eight individuals who doubled their fluid intake on the second test showed no greater variation in their curve than those on a constant intake. This agrees with the findings of Rowntree and Shaw but not with those of Sugimura,<sup>10</sup> who noted an increase of about 5 per cent in the first 30 minutes' excretion while the subjects were forcing fluids.

Snowden has stated that the excretion of phenolsulphonephthalein is definitely increased in severe nephritis when the urine volume is increased. To estimate the effect of an increase in urine volume on the output of dye by such diseased kidneys we have repeated the fractional phenolsulphonephthalein tests on 4 patients with Bright's disease while they were forcing fluids. Under these conditions we find no significant changes in the dye output.

**The Fractional Phenolsulphonephthalein Test in Bright's Disease.** In the past 2 years we have used this test in a large number of patients with suspected renal disease. From this group we have selected all cases with a clinical diagnosis of Bright's disease in whom both the fractional phenolsulphonephthalein and the urea

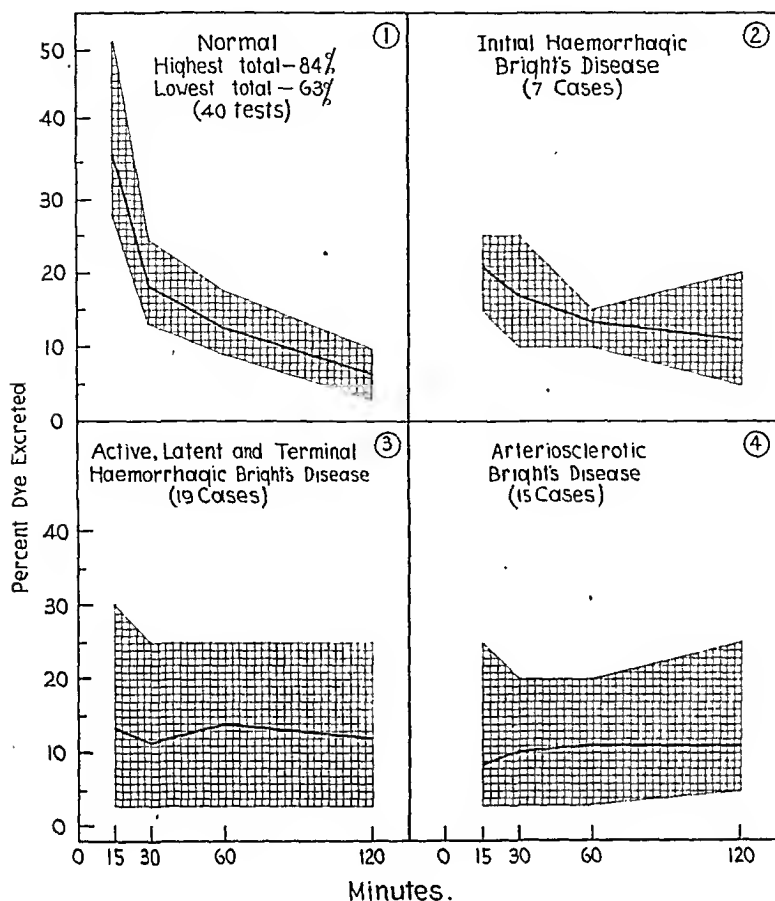


FIG. 1.—The variations and the average curve of phenolsulphonephthalein excretion in normal persons and in those with Bright's disease.

TABLE 1.—THE RELATION OF URINE VOLUME TO THE OUTPUT OF DYE BY DISEASED KIDNEYS.

No.	Fluid intake, cc.	Fractional 'phthalein.					Total urine volume, cc.	Date.
		Per cent dye.				Total.		
		Minutes.						
		15	30	60	120			
32 . . . . .	400 1200	10 5	10 10	.. 15	25 12	45 42	275 770	2- 4-32 2-15-32
36 . . . . .	400 1500	10 10	5 5	10 10	5 15	30 40	175 515	2-12-32 2-15-32
22 . . . . .	400 1600	5 5	3 3	5 10	5 10	18 30	410 1275	2-15-32 2-16-32
17 . . . . .	600 2000	10 15	5 5	10 5	15 12	40 37	170 785	4-25-32 4-27-32

clearance tests were performed. No patients with congestive cardiac failure or with extrarenal factors, such as liver disease,<sup>4</sup> or the recent ingestion of magnesium sulphate\* were included.

Forty-three such cases are grouped according to the Addis classification of Bright's disease<sup>1</sup> as follows: hemorrhagic, 26; arteriosclerotic, 15; degenerative, 2.

We have divided hemorrhagic Bright's disease into 2 groups in the tables. The first group corresponds to acute glomerular nephritis and the second to the chronic form. Arteriosclerotic Bright's disease includes all cases in which the lesion is essentially vascular and thus includes the malignant hypertension of comparatively young people, of which there are 7 cases in our group of 15. Degenerative Bright's disease corresponds to lipoid nephrosis, amyloidosis and the nephritis of chemical and toxic poisoning.

**Analysis of Data.**—In the tables we have listed the significant urinary findings, the range of specific gravity, the blood non-protein nitrogen and the 2 tests done on each patient. The specific gravity was obtained in most instances from concentration tests, but in a few, further information of the ability of the kidney to concentrate the urine was gained from single urine examinations.

The urea clearance tests were performed according to the method described by Moeller, McIntosh and Van Slyke.<sup>7</sup> The values for the 2 specimens of urine usually checked within 10 per cent and corrections for body weight<sup>8</sup> were made for children. The normal range of this test in the standard clearance (where the urine volume is less than 2 cc. per minute) is from 76 to 121 per cent, so that any figure below 76 per cent indicates diminished renal function. In the maximum clearance (where the urine volume is above 2 cc. per minute) the normal range lies between 85 and 132 per cent.

The fractional phenolsulphonephthalein tests were done as part of the routine laboratory work, using Hynson, Westcott and Dunning standards, and the same technique was used as described for the normals except that the patient drank 400 to 500 cc. of water and the 45-minute specimen was omitted. Only occasionally was a patient unable to void at the stated intervals. No normal person excreted less than 28 per cent of dye in the first 15 minutes, but we have taken 25 per cent as the lowest limit of normal in the patients. Although the lowest total output in 2 hours in the normal group was 63 per cent, we have considered 55 per cent as normal in our analysis of cases for two reasons: (1) This is generally accepted; (2) Van Slyke *et al.* used this figure in their comparison of the urea clearance with the phenolsulphonephthalein test.

Analysis shows that there is some agreement of the range of specific gravity and the non-protein nitrogen with the urea clearance

\* Macht<sup>6</sup> has shown that the ingestion of magnesium sulphate delays the elimination of phenolsulphonephthalein, the effect lasting 3 to 4 hours after ingestion.

and fractional phenolsulphonephthalein tests. In the 43 cases we find that the specific gravity was below 1.024 in 21, the non-protein nitrogen was above 40 mg. per 100 cc. in 25, the urea clearance test indicated impaired renal function in 29 cases and the fractional phenolsulphonephthalein in 35. Inasmuch as we are primarily interested in the fractional phenolsulphonephthalein and the urea clearance tests, we shall consider only these two.

TABLE 2.—INITIAL HEMORRHAGIC BRIGHT'S DISEASE.

(Cs Indicates Standard Urea Clearance; Cm Indicates Maximum Urea Clearance.)

No.	Sex, age.	Urine.					NPN.	Fractional 'phthalein.						Urea clearance, per cent of normal av.	
		Alb.	R.B.C.	Casts.	Range of sp. gr.	Per cent excreted.					Date.	Date.			
						Minutes.				Total.					
						15.		30.	60.				120.		
1	F 37	+	+++ ○	+	1.016 1.018	32	25 30	10 18	15 15	10 10	60 73	5-16-31 5-24-32	51% Cm 94% Cs	5-25-31 6-10-32	
2	M 15	+++	++	+	1.010 1.028	41 27	20	25	15	15	75	3-19-31	144% Cm	3-18-31	
3	M 6	++	+++	+++	1.012 1.024	46 39	20	25	15	.	60 (1 hr.)	5-28-31	42% Cs	5-27-31	
4	M 14	++++	++++	++++	1.014	27	20	25	15	5	65	1-27-32	135% Cs	1-20-32	
		++++	++++	++++	1.026	35	20	20	10	5	55	2-19-32	135% Cs	2-25-32	
							17	23	15	.	55 (1 hr.)	7-22-32	116% Cm	7-22-32	
5	M 43	++	+++	++++	1.010	85	20	15	15	12	60	5-27-30	48% Cs	5-28-30	
		++	+	++	1.034	35	25	15	13	10	63	6-18-30	47% Cm	6-24-30	
							23	25	15	10	73	7-17-30			
6	M 15	+	++	+++	1.003 1.024	34 23	20	15	15	20	70	12-19-30	107% Cs	12-18-30	
7	M 14	++++	++++	++	1.010	104	15	10	10	5	40	11-1-31	50% Cs	11-2-31	
		○	+	+	1.020	60	30	15	..	45 (½ hr.)		11-15-31	122% Cs	11-18-31	
						34									

In Table 2 (initial hemorrhagic Bright's disease) the first 6 of the 7 cases had an output of phenolsulphonephthalein of at least 55 per cent in 2 hours. This would be considered normal if it were the only information we had concerning the excretion of the dye. However, using the fractional method, we find that there is a delay in the elimination of the dye, which we interpret as indicating diminished kidney function, in all of these except Case 1, whose 15-minute excretion was 25 per cent. In only 3 of the 6 (Nos. 1, 3, 5) did the urea clearance indicate impaired function. In 1 case (No. 1) the urea clearance alone indicated diminished function, but a year later both tests gave higher values.

Case 7, a boy, aged 14 years, entered the hospital in convulsions. Both the fractional phenolsulphonephthalein and the urea clearance

tests, performed several days later when he was able to coöperate, were below the normal variations. Two weeks later when he was clinically improved and albuminuria had disappeared, both tests had returned to normal.

TABLE 3.—ACTIVE, LATENT AND TERMINAL HEMORRHAGIC BRIGHT'S DISEASE.

No.	Sex, age.	Urine.				NPN.	Fractional 'phthalein.						Urea clearance, per cent of normal av.	
		Alb.	R.B.C.	Casts.	Range of sp. gr.		Per cent dye.					Date.		Date.
							Minutes.				Total.			
							15.	30.	60.	120.				
8	M 49	+++ ++	++++ ++++	++ ++	1.005 1.019	40 ...	25 25 25	25 .. 15	15 .. 15	10 .. 15	75 .. 55	1-10-32 1-14-32 7-1-32	130% Cm 98% Cs	1-14-32 7-11-32
9	F 33	+++	+	+	1.018 1.024	26	25	20	20	10	75	6-12-32	76% Cs	6-14-32
10	M 50	+++	+	++++	1.015 1.024	29	25	15	15	5	60	11-1-31	85% Cs	11-10-32
11	M 40	++++ ++++	++ ++	++++ ++++	1.018 1.026	35	30 8	10 12	10 18	10 15	60 53	12-9-31 6-3-32	93% Cs 53% Cs	12-10-31 7-1-32
12	M 26	++++	+++	++	1.010 1.020	26	20	15	15	15	65	10-10-30	39% Cs	11-6-30
13	F 38	○ +	+	+	1.006 1.025	53 46	10 20	10 10	20 20	25 ..	65 50 (1 hr.)	5-16-31 8-10-32	51% Cm 92% Cs	5-21-31 9-9-32
14	F 15	++++	+	+++	1.012 1.022	39 59	10	15	15	20	60	12-19-30	50% Cs	12-19-30
15	F 27	+	+	○	1.002 1.014	72 41	15	..	25	15	55	3-20-31	23% Cm	4-6-31
16	F 14	++++	+	+++	1.008 1.024	35	10	15	15	15	55	12-27-31	51% Cs	12-24-31
17	M 53	++++	+	+	1.016 1.022	36 ..	15 10 8	13 5 12	15 10 15	15 15 ..	58 40 35 (1 hr.)	4-21-32 4-25-32 6-20-32	80% Cs 104% Cm	4-23-32 7-1-32
18	F 20	++++ ++++	++ +	++++ ++	1.010 1.030	29 ..	15 5	15 10	15 15	.. 15	45 (1 hr.) 45	12-16-31 7-7-32	77% Cs 91% Cs	12-2-31 7-8-32
19	F 22	++	○	+	1.010 1.018	44	17	10	15	..	37 (1 hr.)	6-4-32	50% Cs	6-6-32
20	M 30	+++	++++	++++	1.010 1.024	48 31	3	5	25	10	43	3-19-32	89% Cs	3-9-32
21	F 15	++++	+	++++	1.014 1.032	25 44 63	5	5	8	8	26	11-2-31	41% Cs	12-9-31
22	F 25	++	+	+	1.010 1.020	38 ..	3 5	5 3	3 5	8 5	19 18	1-22-32 2-15-32	44% Cm	2-3-32
23	F 59	++++	○	++++	1.012 1.024	60 50	3 ..	3 ..	3 ..	3 ..	12 .....	11-29-31 .....	18% Cs Died	12-2-31 9-10-32
24	F 44	+	+	+++	1.010 1.014	95 70	0 ..	0 ..	0 ..	0 ..	0 .....	6-17-31 .....	19% Cs Died	6-10-31 7-13-31
25	M 23	++++	++	++++	1.010 1.020	70 ..	5 ..	5 ..	5 ..	10 ..	25 .....	9-21-31 .....	18% Cs Died	10-14-31
26	M 17	++++	+	++	1.008 1.015	180 ..	0 ..	3 ..	3 ..	3 ..	9 .....	3-11-32 .....	8% Cs Died	3-14-32 4-14-32

The tests in Case 4 are interesting because the patient entered in the initial stage and progressed into the active chronic stage with persistence of hematuria and albuminuria. During this time 3 comparative tests were done. The fractional phenolsulphonephthalein tests showed progressive impairment whereas the urea clearance remained normal.

TABLE 4.—ARTERIOSCLEROTIC BRIGHT'S DISEASE.

No.	Sex, age.	Urine.				NPN.	Fractional 'phthalein.						Urea clearance, per cent of normal av.	
		Alb.	R.B.C.	Casts.	Range of sp. gr.		Per cent dye.				Date.		Date.	
							Minutes.							Total.
							15.	30.	60.	120.				
27	F 35	+	○	○	1.006 1.020	37 27	25 ..	20 ..	20 ..	15 ..	80 .....	5-27-31 .....	57% Cs Died	5-27-31 3-3-32
28	F 29	+++ +++	○ ○	++ ○	1.010 1.030	59 ..	8 tr	15 3	8 5	20 5	51 15	11-30-30 6-27-32	59% Cs 35% Cs	12-1-30 6-27-32
29	F 67	++	++	+++	1.010 1.018	76 60	15	10	15	10	50	5-14-31	52% Cs	5-15-31
30	M 50	+	○	+	1.018 1.028	38	12	15	15	10	52	11-3-30	65% Cs	11-5-30
31	F 36	++	○	++	1.013 1.020	25	8	20	10	10	48	11-11-30	79% Cm	11-17-30
32	M 38	+++	+	++	1.010 1.016	36 65	15 10 3	20 10 3	10 .. tr	10 25 5	45 45 10	1-29-32 2-4-32 3-22-32	63% Cs 35% Cm Died	2-4-32 3-22-32 6-1-32
33	F 50	++	○	○	1.006 1.020	83 50	5	10	15	15	45	3-14-31	31% Cs	3-16-31
34	M 47	+++	+	+	1.012 1.024	45 64	5	15	10	10	40	1-17-31	72% Cs	1-13-31
35	F 22	+++	+	+	1.008 1.025	22 ..	10 ..	5 ..	10 ..	10 ..	35 .....	10-9-30 .....	37% Cs Died	10-10-30 12-13-30
36	F 45	+++	+	○	1.001 1.016	46	5	5	5	10	25	6-14-32	70% Cs	6-13-32
37	F 32	+++	○	+	1.010 1.020	64 ..	3 ..	3 ..	3 ..	5 ..	14 ..	2-5-32 ..	39% Cs Died	2-8-32 7-22-32
38	M 40	+++	+	++	1.008 1.024	47 59	10 ..	5 ..	10 5	5 13	30 18	2-12-32 4-2-32	122% Cs 67% Cs Died	2-15-32 4-5-32 6-27-32
39	F 41	++	+	+	1.012 1.024	36 ..	15 ..	15 ..	10 ..	15 ..	55 ..	10-20-30 ..	50% Cs Died	11-12-30 3-31-31
40	F 55	++	+	++++	1.014 1.020	66	3	..	5	5	13	12-16-31	15% Cs Died	12-21-31 3- -32
41	F 49	+++	+	++	1.009 1.012	130 ..	3 ..	0 ..	3 ..	3 ..	9 ..	12-14-31 ..	7% Cs Died	12-14-31 5- -32

From Table 3 we find that the first 10 patients (Nos. 8 to 17) had at least 55 per cent output in 2 hours; 6 of these (Nos. 12 to 17) showed abnormal fractional tests, with a delay in the excretion



of dye. The remainder of the group (Nos. 18 to 26) all showed rather marked kidney impairment by the fractional test and the total output was well below 55 per cent. In all except 3 of the patients (Nos. 17, 18, 20) both the urea clearance and the fractional phenolsulphonephthalein tests agreed. In these only the latter test indicated a diminished function. We have been able to repeat the tests at intervals of several months on Patients 8, 11, 13, 17 and 18. In Patient 8 the tests were normal on both occasions, although albuminuria and hematuria were still present at the second examination. The first fractional phenolsulphonephthalein and urea clearance tests were normal on Patient 11, although at that time the patient had considerable edema, albuminuria and a blood pressure of 160 systolic and 100 diastolic. Six months later both tests showed a marked decrease. The total output in the dye test was very little changed, but the fractional readings showed a great difference with a low initial output and a delayed excretion. In Patient 13 both tests showed improvement after a year's interval. Patient 17 showed a slight decline in the fractional test alone. Patient 18 showed a decrease in the fractional phenolsulphonephthalein but the urea clearance increased 14 per cent. Clinically this patient was worse and was having persistent edema to the mid-thighs at the time of the second test.

Of the patients with arteriosclerotic Bright's disease (Table 4) only 2 (Nos. 27, 39) had a total output over 55 per cent. In Patient 39 the excretion of dye was delayed, but in Patient 27 it was normal by the fractional test, yet the urea clearance showed an impaired function.

TABLE 5.—DEGENERATIVE BRIGHT'S DISEASE.

Case 42.—Diagnosis: amyloidosis; tuberculosis of the cecum.

Case 43.—Diagnosis: bichlorid of mercury nephrosis.

No.	Sex, age.	Urine.				N.P.N.	Fractional 'phthalein.					Urea clearance, per cent of normal av.		
		Alb.	R.B.C.	Casts.	Range of sp. gr.		Per cent dye.				Date.	Date.		
							Minutes.							
15	30	60	120	Total.										
42	M 25	++++	0	++++	1.008 1.022	24 ..	15 19	.. 10	30 ..	15 ..	60 20 (4 hr.)	12-12-31 12-18-31	102% Cs	12- 7-31
43	M 39	++	0	+	1.005 1.024	30 ..	15 20	35 35	15 17	.. 3	65 75	5-28-32 6-3-32	96% Cs	5-31-32

Comparative tests done after a lapse of months in Patients 28 and 32 showed a diminished kidney function by both tests, although a greater diminution was reflected by the fractional phenolsulphone-

phthalein. In Patient 38 the urea clearance test at the first period of study showed a high normal but a very low fractional phenolsulphonephthalein test. Two months later the patient became much worse and the urea clearance was reduced one-half. He died shortly thereafter.

The effect of a high blood pressure on the excretion of phenolsulphonephthalein remains an unsettled problem. Lundsgaard and Moeller<sup>5</sup> believe that the dye output may be decreased in the presence of a high blood pressure. We have encountered patients with hypertension without congestive failure who had depressed curves of phenolsulphonephthalein excretion but with few or no other signs of kidney disease. However, we have observed normal fractional phenolsulphonephthalein tests in as many patients with hypertension in whom there was no evidence of Bright's disease.

In Table 5 are listed the 2 cases of degenerative Bright's disease. In both of these there was a delay in the elimination of phenolsulphonephthalein, yet the total output of the dye and the urea clearance were normal.

**Discussion.** In summing up we find that 14 patients (32.5 per cent) with a total dye output of 55 per cent or more had a delay in the elimination of phenolsulphonephthalein. This group represents cases that would be judged to have a normal excretion of dye by the old method of hourly collections, but this delay shown by the fractional method indicates a diminished renal function. The charts in Fig. 1 show the variations and the average curve of dye excretion in normal persons and in those with Bright's disease. As the renal lesion progresses it is apparent that the curve tends to flatten out.

In a comparative study of the urea clearance test with the 2-hour output of phenolsulphonephthalein after intravenous injection, Van Slyke *et al.* have shown that when the urea clearance is between 40 and 60 per cent of normal average function about one-half the phenolsulphonephthalein outputs are above and one-half below 55 per cent of the dye injected. We find this to be true of our cases, but an analysis of the 8 cases (Nos. 1, 3, 5, 13, 14, 16, 27, 39) with the phenolsulphonephthalein output above 55 per cent and the urea clearance between 40 to 60 per cent shows that all but 2 (Nos. 1, 27) had a delayed excretion of dye indicating impairment of kidney function and thus agreeing with the urea clearance test. On the other hand, there were 9 patients (Nos. 2, 4, 6, 17, 18, 20, 38, 42, 43) in whom the urea clearance was 76 per cent or above and yet the fractional phenolsulphonephthalein test showed a diminished function.

Of the 12 patients in whom repeated tests were done later in the course of their disease we find that 5 (Nos. 7, 11, 13, 28, 32) had approximately parallel changes in both the urea clearance and the

fractional phenolsulphonephthalein tests. In 3 (Nos. 4, 17, 18) a decrease in the kidney function of patients with active hemorrhagic disease was shown only by the phenolsulphonephthalein test. In 2 (Nos. 1, 5) the urea clearance gave a better indication of the changes in function. In 1 (No. 8) both tests were normal.

*It is particularly significant, on review of all cases, that an abnormal elimination of the dye was reflected chiefly in the first 15-minute specimen, and so this is by far the most important. For the general practitioner and in the out-patient department this determination alone would be sufficient in most cases.* It is, of course, essential to know that there is no urinary retention and that the patient has completely emptied the bladder. Finally it should be emphasized that the fractional phenolsulphonephthalein test is a simple procedure, not requiring the aid of a chemical laboratory, and in our experience is more practical than the urea clearance test.

**Summary and Conclusions.** The fractional method of estimating the elimination of phenolsulphonephthalein (15, 30, 60 and 120 minutes) has been studied in the past 2 years in 20 normal subjects and a large number of patients with suspected renal disease.

We have found that in Bright's disease the fractional test may show evidence of impaired renal function when the test as usually done, with hourly collections, is interpreted as normal.

This fractional test is quite as informative as the urea clearance test and reflects the diminishing function in progressive kidney disease.

Since it is easier to perform, it is the method of choice for routine clinical work.

We wish to thank Miss Clara Durgin for assistance in performing the urea clearance tests.

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## NORMAL VARIATIONS IN RENAL FUNCTION TESTS WITH DISCUSSION OF THEIR PHYSIOLOGIC SIGNIFICANCE.

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IN order to estimate the value of kidney function tests in renal disease it is important to know what function of the kidney each test measures and how great a departure from normal must occur before abnormal function can be revealed. Most tests in clinical use today are able to indicate at best gross damage to the kidney, and physicians make little attempt to separate them according to the type of disturbed kidney physiology. Albuminuria, for example, is due to a different physiologic mechanism than is an inability of the kidney to concentrate urine, but both abnormalities frequently are interpreted as signs of nephritis without thought as to their underlying cause.

One great obstacle to the scientific classification of renal function tests is the delay in accepting the Ludwig theory of urine formation of filtration through the glomeruli with a reabsorption of fluid and solids in the tubules, as set forth by Cushny<sup>1</sup> and verified by the direct observations of Richards and his colleagues.<sup>2</sup> According to this theory, which we have adopted as a working hypothesis, in the glomeruli a process of filtration takes place whereby all of the constituents of the blood plasma except the proteins pass into the glomerular filtrate in the same concentration as they exist in the plasma. As this filtrate passes down the tubules most of the water is reabsorbed into the blood. The solid waste elements of the filtrate return through the tubular walls in greater or less extent. Thus creatinin, to which the tubular cells are apparently impermeable, probably is not appreciably reabsorbed, whereas about 50 per cent of the urea is reabsorbed. Certain substances present in the plasma, however, normally appear in the urine either not at all or in less concentration than in the plasma. These elements, such as glucose and chlorids, known as threshold substances, cannot be reabsorbed in the tubules by a simple process of back diffusion, but by a specific activity of the tubular cells.

In order to account for the degree of concentration of some of the substances in the urine of man, Rehberg<sup>3</sup> has calculated that a

glomerular filtration of from 100 to 200 cc. per minute is necessary. Since the urinary output under normal conditions rarely exceeds 1 to 2 cc. per minute, it is obvious that about 99 per cent of the water may be reabsorbed by the tubules. To estimate the amount of glomerular filtration Rehberg employs creatinin as an index, since there is indirect evidence that little or none of this substance is reabsorbed in its passage down the tubules. If the concentration of creatinin in the blood and urine and the urinary excretion per minute are known, then, as creatinin concentration in the glomerular filtrate and plasma is identical,<sup>2</sup> the ratio of the percentage of urine creatinin to plasma creatinin represents the degree to which the glomerular filtrate is concentrated. This value is known as the *concentration index*. The amount of glomerular filtrate formed per minute is, therefore, equal to this concentration index times the urinary excretion and can be determined from the formula:

$$\text{Glomerular filtrate} = \frac{\text{urinary concentration creatinin}}{\text{plasma concentration creatinin}} \times \text{urine formed per minute.}$$

Under abnormal conditions, alterations in the formation of urine may occur from disturbances of: (1) filtration and (2) reabsorption. In studying the function of the kidneys clinically, it is desirable to obtain a separate estimate of these two functions. Filtration may be lessened by: (a) Diminution in the glomerular blood pressure; (b) a decrease in permeability of the glomerular membrane; or (c) a reduction in cross-sectional area of the filtering surface due either to damage to individual glomeruli or to a reduction in the total number of glomeruli. Reabsorption of fluid may be lessened either because of an increased volume of filtrate flowing down the tubule or as a result of damage to the tubular cells.

**Clinical Methods for Determining Altered Renal Function.** 1. *Glomerular Function.* The creatinin clearance procedure of Rehberg gives a direct indication of the amount of glomerular filtration. The urea clearance test under conditions of maximal excretion also gives a relative index of the degree of filtration, since with urinary excretions exceeding 2 cc. per minute the percentage of back diffusion of urea through the tubules is nearly constant. When the urea and creatinin clearance are performed simultaneously, it is possible to compute the percentage of urea reabsorbed by the tubules and thus detect any increased permeability which may occur.

In the advanced stages of renal disease the glomerular filtration is so much decreased that the kidneys are unable to maintain an adequate excretion of nitrogenous and other waste products. These substances are, therefore, found in abnormally high concentration in the blood plasma. In clinical practice the usual tests are for the total nonprotein nitrogen, urea nitrogen, creatin, creatinin and uric acid of the blood.

The presence of albumin in the urine indicates an abnormal permeability of the glomerular membrane to protein, and the presence of red blood corpuscles is due either to increased permeability or to rupture of capillaries. Casts are found as the result of inflammatory changes and are due to the coagulation of protein and cells which have passed into the lumina of the tubules.

2. *Tubular Function.* The ability of the tubules to reabsorb water is best measured by procedures which concentrate the urine to as high a degree as possible. The capacity of the tubular cells to absorb threshold substances actively can be examined by estimating the concentration of one or more of these solids in the blood and urine.

**Purpose of Investigation.** In order to correlate a study of several simultaneously applied clinical technical procedures with the physiologic functions which they estimate and to show how fluctuation in one test may affect the outcome of other tests, we have studied a group of normal young adults, none of whom had albuminuria or an abnormal urinary sediment.

**Methods.** The subjects were in a fasting state and remained in bed throughout the test periods except when the concentration tests were made.

(a) *Creatinin Clearance.* The technique of Rehberg<sup>3</sup> with unimportant modifications was followed. Three grams of creatinin were fed 1½ hours before the urine collection period began. The plasma creatinin was determined by the method of Folin and Wu<sup>4</sup> using picric acid purified according to Benedict's directions.<sup>5</sup> The urine creatinin was determined by Folin's method.<sup>6</sup> The calculation of the glomerular filtrate was made according to the formula previously stated. The values for plasma creatinin found in the samples taken before and after each hourly test period were averaged.

The terms "creatinin clearance" and "urea clearance" have been employed, because such a term was suggested by Van Slyke for the urea procedure and we have used his formulae in expressing our values. The "creatinin clearance" is synonymous with the term "glomerular filtrate."

(b) *Urea Clearance.* This was usually determined simultaneously with the creatinin clearance. The analyses for urea were carried out on whole blood and urine by Van Slyke's gasometric extraction method.<sup>7</sup>

The urea clearance per minute when the urinary excretion exceeded 2 cc. per minute was calculated from the same formula as creatinin, substituting urea for creatinin. Seventy-five cc. was taken as the theoretical normal. This is called the "maximum clearance."

When the diuresis falls below 2 cc. per minute Van Slyke and his co-workers<sup>8</sup> have suggested that the formula is best expressed by taking the square root of the urinary minute volume rather than the total urinary minute volume. This determination is called the "standard clearance." In the few cases (Table 1) where the diuresis fell below 2 cc. per minute, the actual urea clearance values were calculated from the formula for maximal clearance for the sake of uniformity. In these cases, however, figures for the percentage of normal in the same table were calculated from the standard clearance formula, taking 54 cc. as the theoretical normal.

(c) *Concentration Test.* A modification of the Volhard and Strauss tests for the concentration and dilution of urine similar to that suggested by Pratt<sup>9</sup> was employed. The only fluid permitted was 1500 cc. of water

at the beginning of the test. The output in the first 4 hours, the total day and the total night outputs were determined and the specific gravities of the individual samples were measured.

TABLE 1.—THE VALUES OF THE CREATININ AND UREA CLEARANCES OBTAINED IN NORMAL INDIVIDUALS.

Subject.	Age.	Urine, cc. per min.	Creatinin.		Urea.			Blood urea nitrogen, mg. per cent.
			Conc. index.	Filtrate, cc. per min.	Clear- ance, cc. per min.	Per cent of normal.	Excre- tion,* per cent.	
1 . . . . .	31	0.76	179	136	56	118†	38	10.2
		1.40	89	125	69	108†	52	
2 . . . . .	44	2.42	60	135	61	81	39	15.2
		7.00	22	154	67	90	40	
3 . . . . .	31	4.75	36	172	112	149	60	7.4
		8.00	17	136	119	158	81	
4 . . . . .	22	8.93	17	154	70	93	42	9.0
		11.05	14	153	77	102	46	
5 . . . . .	41	0.40	301	120	34	99†	26	11.8
		2.25	57	129	70	94	51	
6 . . . . .	34	1.50	108	162	64	119†	44	11.5
		4.28	42	180	96	128	50	
7 . . . . .	26	2.17	67	145	68	91	43	9.0
		8.26	15	122	54	73	40	
8 . . . . .	38	7.50	16	117	48	64	37	7.9
		11.00	7	79	66	85	79	
9 . . . . .	35	7.09	20	141	80	108	53	15.6
		9.16	14	125	92	122	68	
10 . . . . .	29	1.28	125	160	64	105†	37	10.3
		3.50	49	170	81	108	43	
11 . . . . .	29	3.78	43	164	100	134	57	11.0
		4.67	31	146	98	130	61	
12 . . . . .	45	7.33	30	220	109	145	46	7.9
		6.57	29	180	97	129	47	
13 . . . . .	22	1.63	...	...	70	102†	..	8.9
		8.33	...	...	69	82	..	
14 . . . . .	24	5.66	...	...	63	85	..	13.2
		9.47	...	...	58	77	..	

\* Calculated according to Rehberg,<sup>3,14</sup> corrected for plasma urea nitrogen.

† Per cent of normal calculated by formula for "standard clearance" =  $\frac{U\sqrt{V}}{B}$ . All the other per cents of normal are on a basis of "maximum clearance" =  $\frac{UV}{B}$ .

**Results. Creatinin and Urea Clearance.** Creatinin and urea clearance tests were carried out simultaneously in 12 subjects (Table 1). The creatinin filtrate varied from 117 to 220 cc. per minute with one exception probably due to technical error. These figures are in accord with Rehberg's and average slightly less than those given by Cope<sup>10</sup> for 1 normal male.

In the same 12 subjects and in 2 more, urea clearance measurements were made. These varied from 48 to 119 cc. per minute. When expressed in terms of percentage of normal, assuming a maximum clearance of 75 and a standard clearance of 54 to be nor-

mal, the figures ranged from 64 to 158 per cent. In the cases with a clearance of 64 and 73 per cent, second determinations, respectively, showed 85 and 91 per cent of normal.

Although a rough parallelism was found to exist between the levels of the creatinin and urea clearance, this did not hold with any exactitude. Most of the discrepancy probably was due to the experimental error of the methods, but it is quite possible that fluctuations were caused by individual variations which permitted the urea to diffuse in different proportions back through the tubules to the blood.

Our observations are in agreement with Rehberg that the glomerular filtrate measured by the creatinin test is essentially constant irrespective of the urine volume. This constancy also holds for the urea clearance when the diuresis exceeds about 2 cc. per minute, as has been noted by Van Slyke.<sup>8</sup> When, however, the diuresis falls below this rate the percentage excretion of urea becomes progressively less, with a consequent decrease in the urea clearance. Our observations also suggest that the percentage excretion of urea varies between individuals even under identical conditions.

In order to ascertain whether the oral administration of urea or creatinin increased the urea clearance values, 9 subjects were tested. The results (Table 2), in accord with those of Addis and Drury,<sup>11</sup> indicate that there is no tendency for either urea or creatinin to increase the urea clearance, or, by inference, the creatinin clearance either. There was some fluctuation in the consecutive hourly determinations in spite of the maintenance of conditions as constant as possible. This is particularly marked in Subject 19. In only 4 instances did the urinary output fall below 2 cc. per minute. This low urine output accounts for the low clearance values found in Subject 7 when urea was fed.

It is desirable in the carrying out of both the creatinin and urea clearance procedures in clinical practice to have conditions made as constant as possible. That is, an adequate diuresis of at least 2 cc. per minute should be insured by having the subject drink 400 cc. or more water each hour before and during the test periods. The patient should be kept quiet in bed and preferably should be in the fasting condition.

*Concentrating Power of Tubules.* Dilution concentration tests were carried out in 5 subjects (Table 3). Even with normally functioning kidneys the results may be modified by such factors as the position and activity of the individual, the degree of hydration or dehydration and the elimination of fluid by other channels. It is probable that one or more of these factors was responsible for the lack of urine dilution below a specific gravity of 1.007 in Subject 15, and for the failure of 3 of the 5 subjects (Nos. 10, 17 and 18) to excrete all or nearly all of the 1500 cc. of water ingested within 4 hours. For clinical purposes, however, the value of this



test consists not so much in the total urinary output or the hourly variation in it as it does in the range of specific gravity through which the urine varies and particularly in the maximum specific gravity to which the individual can concentrate urine. It is this that shows the capacity of the tubules to reabsorb water. Practically all normal individuals can concentrate urine to a specific gravity of 1.025 or more.

TABLE 2.—THE EFFECT OF FEEDING CREATININ AND UREA ON THE UREA CLEARANCE OF NORMAL INDIVIDUALS.

Subject.	Urea clearance.			Urine, cc. per min.
	Nothing fed. cc. per min.	Creatinin fed 3 gm. cc. per min.	Urea fed 30 gm. cc. per min.	
10 . . . . .	76	...	...	5.3
	80	...	...	4.9
		64	...	1.3
		81	...	3.5
			80	3.0
			77	5.7
12 . . . . .	102	...	...	3.8
	100	...	...	12.5
		109	...	7.3
		97	...	6.6
			92	2.3
			89	3.5
19 . . . . .	116	...	...	7.7
	73	...	...	2.3
		93	...	5.4
		77	...	2.5
			123	11.0
			83	6.8
11 . . . . .	93	...	...	12.1
	75	...	...	7.5
		98	...	4.7
		100	...	3.8
13 . . . . .	70	...	...	1.6
	69	...	...	8.3
			65	5.0
			60	12.3
7 . . . . .			57	12.3
		68	...	2.2
		54	...	8.3
			36	1.0
8 . . . . .			38	0.9
		48	...	7.5
		66	...	11.0
			62	9.0
9 . . . . .			62	13.6
		80	...	7.1
		92	...	9.2
			111	10.9
			83	12.0
14 . . . . .			85	11.2
		63	...	5.7
		58	...	5.7
			57	4.4
			52	9.5
			48	8.8

TABLE 3.—THE RESULTS OF DILUTION-CONCENTRATION TESTS IN 5 NORMAL INDIVIDUALS, SHOWING VARIATION IN URINE OUTPUT, SPECIFIC GRAVITY, CONCENTRATION INDEX AND GLOMERULAR FILTRATE.

Subject.	Age.	4-hour output, cc.	Day output, cc.	Night output, cc.	Total output, cc.	Specific gravity.		Concentration index.		Filtrate.	
						Low-est.	High-est.	Low-est.	High-est.	Low-est, cc.	High-est, cc.
10	29	685	925	410	1325	1.001	1.036	10	226	26	97
15	33	1030	1580	220	1800	1.007	1.030	16	243	74	180
16	25	1225	1390	285	1675	1.001	1.033	8	270	54	102
17	33	850	1190	340	1530	1.001	1.031	10	160	65	120
18	28	965	1220	380	1600	1.002	1.026	11	137	54	89

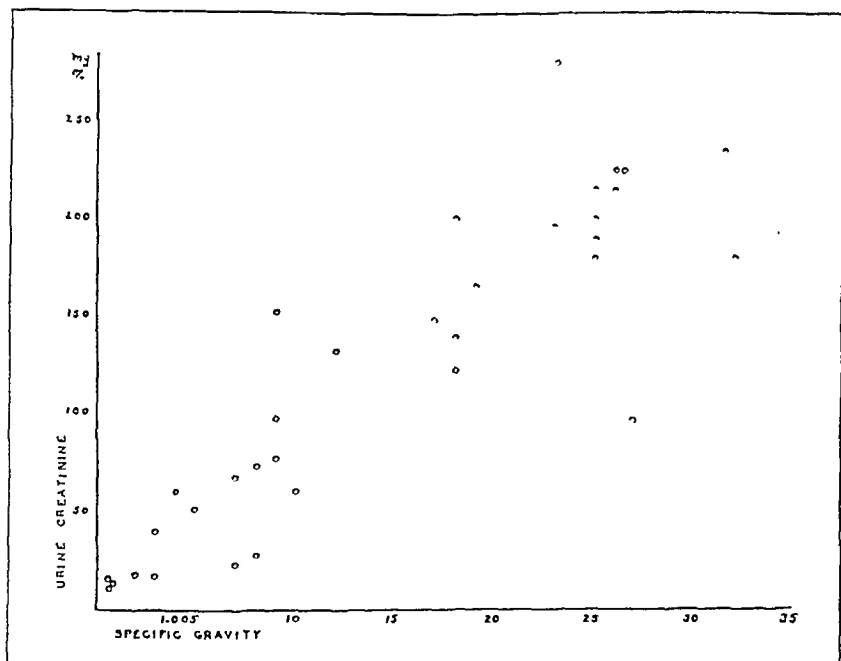


CHART I.—The relationship of the variation in urine specific gravity and creatinin concentration in normal individuals.

*Daily Variation in Glomerular Filtrate.* In conjunction with the dilution-concentration test, the glomerular filtration during each of the collection periods was calculated to ascertain what changes took place when urine was passed which varied from extreme dilution to marked concentration. No creatinin was fed. Only 1 blood creatinin determination was made in each subject. There is evidence that the percentage variation of the plasma creatinin in the same individual at different times is slight.<sup>12</sup> The relationship of the creatinin concentration in the urine to its specific gravity is

depicted in Chart I which shows that these two factors bear practically a linear relationship to each other. That is, under normal circumstances the specific gravity of the urine varies in direct proportion to the amount of creatinin present.

The low values obtained for the glomerular filtrate, we believe, are due largely to the experimental error in determining plasma creatinin at normal levels. Not only is it impossible to determine with accuracy the normal amount of plasma creatinin, but it is quite likely that the results obtained yield values in excess of the true amount.<sup>3,10,13</sup> There is also some evidence that the glomerular filtrate tends to be somewhat higher when the subject is in the prone than in the upright position.<sup>14</sup>

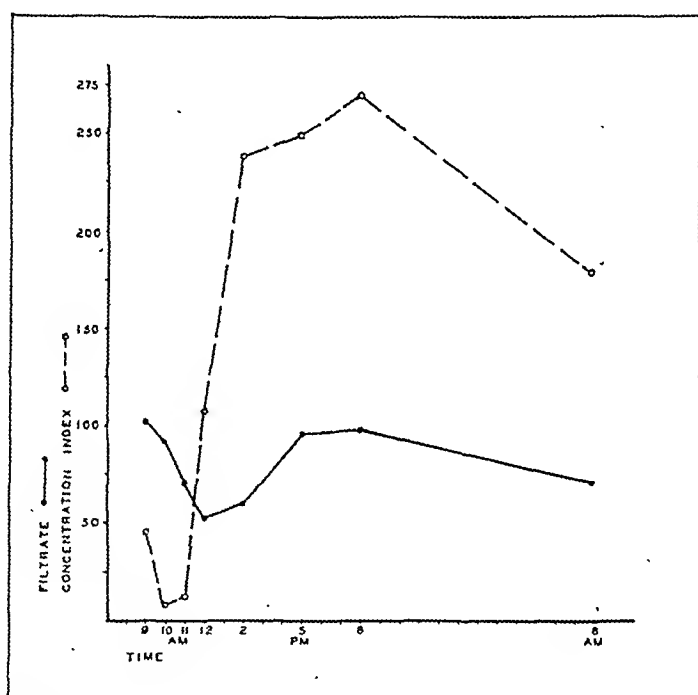


CHART II.—The diurnal variation of glomerular filtrate and of the concentration index during a dilution-concentration test in Subject 16.

Chart II and Table 3 show the relative constancy of the glomerular filtrate when compared with the change in concentration and amount of urine which was noted by Fremont-Smith<sup>15</sup> and others. In other words, the variation in the amount of water excreted and in the concentration of urine is controlled largely by the extent of the reabsorption of water in the tubules.

*Clinical Application of Renal Function Tests.* No single technical procedure is adequate to test thoroughly the function of the kidney. Assuming the correctness of the filtration-reabsorption theory of

renal activity, it is possible to gain information concerning the following processes:

1. Permeability of glomeruli.
2. Glomerular filtration.
3. Tubular reabsorption of fluid.
4. Return of solids through the tubules into the plasma.
5. The "vital" reabsorption of threshold substances.

Except under unusual circumstances there is little value in testing the fourth and fifth processes in cases of inflammatory or vascular nephritis because rarely are they markedly abnormal. However, each of the first three kidney processes should be examined.

Information is gained regarding the permeability of the glomeruli by examination of the urine for albumin, red corpuscles and casts.

The urea or creatinin clearance tests are indices of glomerular filtration. Either test can be employed clinically. It should be appreciated that the reliability of the final results in these procedures is as much dependent on the accuracy in the collection of all the urine passed over an accurately timed period as on the laboratory analysis.

The tubular reabsorptive power is shown by concentration tests of which that of Volhard is a representative example.

Determination of phenolsulphonphthalein excretion is unquestionably valuable to show gross renal change. Examination of the blood for the abnormal retention of nitrogenous and other elements is of value only in the advanced stages of renal disease.

These laboratory procedures are of value only in supplementing clinical observation. They supply worthwhile information only when conducted with care under controlled conditions, and the results obtained require careful interpretation. Moreover, the tests must be repeated frequently if knowledge is to be attained regarding the progression of the disease process.

**Summary and Conclusions.** 1. On 12 normal subjects urea and creatinin clearance tests were performed and on 5 subjects dilution concentration tests were carried out. These studies were made to show the normal variations of each test and the effect of changes in one test on the others, and to correlate the results with the physiologic functions of the kidney which they measure.

2. The creatinin clearance test probably gives a close estimate of the absolute degree of glomerular filtration and the urea clearance provides a relative index of this function. Clinically, either test may be used.

3. The ability of the renal tubules to reabsorb fluid is best measured by a concentration test.

4. To attain as adequate an estimate as is possible by laboratory methods regarding the state of renal function, the tests mentioned together with an ordinary examination of the urine will suffice.

5. At best the information gained from these procedures merely supplements that obtained by the actual clinical observation of the patient.

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## THE RENAL FUNCTION IN PERSONS WITH ONE KIDNEY.

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THE present study concerns the degree of renal function in 12 patients who had undergone unilateral nephrectomy, in 9 of whom the remaining kidney was presumably normal. Such a study, it was hoped, might give information as to (1) the degree of impairment of renal function occasioned by removal of one kidney, and (2) the extent of reduction in functioning kidney tissue which must occur before such a reduction could be detected by laboratory tests.

**Material Studied.**—Nine of the 12 patients, 5 men and 4 women, complained of no symptoms and showed no abnormalities of the cardiovascular renal systems. They were from 16 to 50 years of age. None showed albuminuria or abnormality of the urinary sediment. The operative removal of the kidneys was because of pyonephrosis, hydronephrosis, calculus, tumor or trauma. Three of the cases were studied within 2 weeks of the time of operation and again 4 to 5 months later. In 1 of these patients the kidney was almost completely destroyed by hydronephrosis; but in the other 2, 1

of whom had a tumor and the second a congenital anomaly, the renal tissue, although somewhat reduced in amount, was apparently normal in quality and possessed functioning ability. The remaining 5 cases had had nephrectomies performed from 18 months to 6 years previous to the observations.

Of the 3 who suffered from complications 2 had pyonephrosis involving the remaining kidney, and the third had hypertension.

The technique of the renal function procedures carried out is described in the preceding paper.<sup>1</sup> The urea and creatinin clearance values were determined simultaneously. A modification of Volhard's dilution-concentration test was employed, and the excretion of phenolsulphonphthalein 130 minutes after its intramuscular injection was estimated.

**Results.** The cases have been divided into 5 groups. The division between the 3 groups of longstanding cases without complications is dependent on very slight differences in the results of one or more of the functional tests, but has been made because it facilitates analysis in regard to the physiologic and compensatory changes.

**GROUP 1. *Recent Cases.*** Tests were performed on Cases 1 and 2 within 2 weeks of operation (Tables 1 and 2). Gross and microscopic examination of the removed kidneys indicated that the renal tissue, although somewhat reduced in extent, possessed functioning ability. In both patients the glomerular filtrates determined by the creatinin method were at the lower limit of normal and the urea clearances were reduced to a parallel extent. In these subjects the maximum concentrating power of the kidneys was possibly slightly diminished. The total fluid excretion was normal and the phenolsulphonphthalein excretion was excellent. In both patients the examinations were repeated 4 to 5 months after the operation. The results obtained were almost identical to those obtained shortly after operation.

**GROUP 2. *Cases With Normal Kidney Function.*** In 2 cases (3 and 4) the functional tests were normal (Tables 1 and 2). In Case 3 the kidney was removed 20 months previously. The second patient was studied 2 weeks and again 4 months postoperatively, but since the removed kidney was almost entirely destroyed by hydronephrosis, it is reasonable to assume that he had had but one functioning kidney for some time. For this reason it is doubtful how much, if any, of the improvement which is evident from the tests should be ascribed to compensatory hypertrophy of the intact kidney following operation.

**GROUP 3. *Cases With Questionable Diminution of Concentrating Ability.*** All tests on Cases 5, 6 and 7 were normal except that the patients were unable to concentrate their urine above a specific gravity of 1.020, 1.022 and 1.024 respectively (Tables 1 and 2).

**GROUP 4. *Cases With Disturbed Filtration.*** Two cases (8 and 9) had glomerular filtrates, as calculated by the creatinin clearance test, below the lower limit of normal, 100 cc. per minute (Tables 1 and 2). In these subjects, however, the urea clearance values and the concentrating power of the kidneys were normal.

TABLE 1.—THE UREA AND CREATININ CLEARANCES, THE BLOOD UREA NITROGEN, AND THE PHENOLSULPHONPHTHALEIN EXCRETION IN 12 PATIENTS WITH ONE KIDNEY.

Patient.	Age.	Arterial blood pressure, mm. Hg.	Duration of nephrectomy.	Diagnosis.	Phthalein excretion, per cent.	Urea.		Blood urea nitrogen, mg. per cent.	Creatinin filtrate, cc. per min.	
						Clearance, cc. per min.	Per cent of normal.			
1	16	118/80	8 days	Congenital anomaly of renal pelvis	70	51	72	8	91	No complications
			5 weeks		..	54	72	..	102	
			5 months		75	52	70	10	93	
2	24	115/80	2 weeks	Tumor	65	44	59	..	81	
			4 months		70	56	75	8	113	
			2 weeks		65	56	75	9	86	
3	50	134/84	20 months	Pyonephrosis	45	30*	56	..	132	
			4 months		70	50	67	9	75	
4	18	120/80	2 weeks	Hydronephrosis	50	56	75	9	105	
			4 months		65	46	62	..	103	
5	42	108/76	18 months	Trauma	50	95	127	13	163	
			4 years		45	92	102	..	180	
6	40	112/70	4 years	Pyonephrosis	45	71	95	8	..	
			1 year		65	66	89	..	157	
7	23	114/74	4 years	Pyonephrosis	35	95	127	10	112	
			6 years		75	72	96	13	113	
8	27	110/68	4 years	Pyonephrosis	35	66	85	..	105	
			6 years		75	81	107	5	142	
9	43	120/80	6 years	Calculus	75	75	100	..	132	
			12 years		..	53	70	15	128	
10	47	130/85	12 years	Pyonephrosis	..	65*	121	18	70	
			18 months		20	66*	122	..	65	
11	52	126/76	18 months	Pyonephrosis	20	72	96	12	76	
			9 years		..	70	93	..	90	
12	44	230/135	9 years	Pyonephrosis	..	24	32	14	37	Complications
			9 years		..	20	26	15	34	

\* Urea clearance expressed in terms of "standard" clearance of Van Slyke. All others are "maximum."

TABLE 2.—THE RESULTS OF THE DILUTION-CONCENTRATION TEST IN THE PATIENTS WITH ONE KIDNEY, SHOWING THE URINE EXCRETION AND THE VARIATION IN SPECIFIC GRAVITY, CONCENTRATION INDEX AND GLOMERULAR FILTRATE.

Sub-ject.	4-hour output, cc.	Day output, cc.	Night output, cc.	Total output, cc.	Specific gravity.		Concentration index.		Filtrate.		Time since operation.	
					Lowest.	Highest.	Lowest.	Highest.	Lowest, cc. per min.	High'st, cc. per min.		
1	1100	1370	235	1605	1.002	1.024	7	164	36	54	5 weeks	No complications
	1220	1485	180	1665	1.001	1.024	..	..	..	..	5 months	
2	1140	1500	190	1690	1.001	1.021	..	..	..	..	2 weeks	
	1320	1520	180	1700	1.001	1.023	..	..	..	..	4 months	
3	1130	1414	355	1770	1.002	1.026	11	210	64	195	20 months	
	1270	1724	541	2265	1.001	1.020	..	..	..	..	2 weeks	
4	1210	1735	330	2065	1.001	1.025	9	170	78	108	4 months	
	740	1232	520	1750	1.002	1.030	17	178	52	78	18 months	
5	incomplete	190	..	..	1.002	1.022	8	189	49	133	4 years	
	812	1133	340	1473	1.001	1.024	8	128	41	112	1 year	
6	507	649	89	738	1.002	1.040	7	265	22	66	4 years	
	1100	1375	310	1685	1.002	1.025	8	120	45	57	6 years	
11	556	incomplete	..	..	1.003	1.011	..	..	..	..	18 months	Complications
	734	1194	325	1519	1.003	1.021	8	55	23	44	9 years	

GROUP 5. *Cases With Complications.* The 3 patients (Cases 10, 11 and 12) suffering from complications had had nephrectomies performed previously for pyonephrosis. In 2 of the cases the symptoms and large amounts of pus and albumin in the urine gave evidence that the infection had involved the remaining kidney. In these cases the pathologic process had involved the remaining kidney to an extent sufficient to result in a marked interference with renal function as indicated by the laboratory procedures.

The third patient (Case 12), a man, aged 44 years, on whom a nephrectomy had been performed 9 years previously, had had a known hypertension for 8 years, with gradually increasing cardiac symptoms. All functional tests of his kidneys gave low results. His urine contained much albumin.

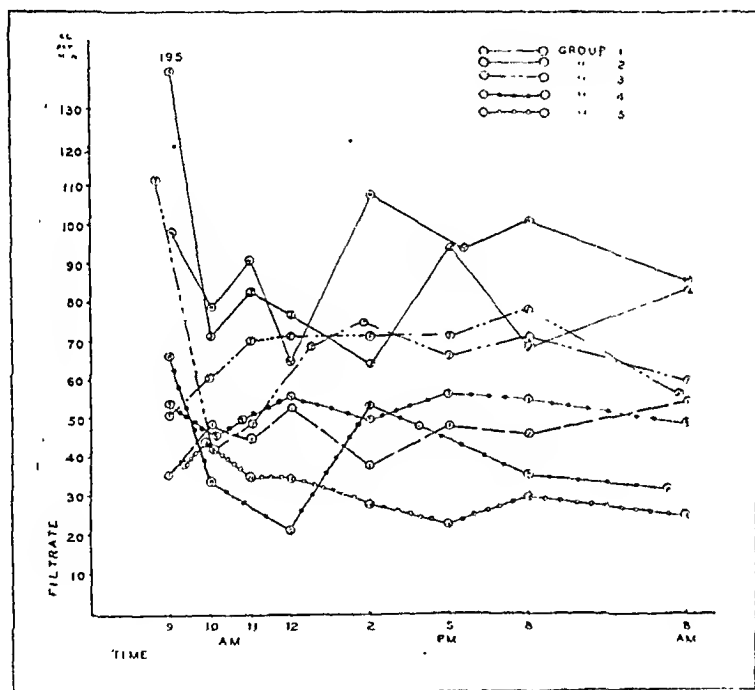


CHART I.—The diurnal variation in glomerular filtrate during a dilution-concentration test in 9 individuals with one kidney.

*Daily Variation in the Filtrate.* In 9 of the cases the glomerular filtrate was determined throughout a 24-hour period in conjunction with the dilution-concentration tests (Chart I). No creatinin was fed during these examinations. The level of the filtrate determined in this way tended to be lower than that obtained by creatinin clearance tests when the same patients were fed creatinin. The probable cause for this finding, observed also in normal persons, has been discussed previously.<sup>1</sup> The glomerular filtrate remained relatively constant compared to the degree of concentration of the



various urine specimens. Thus in persons with one kidney, as in normal subjects, the diurnal variation in the amount and concentration of the urine excreted is chiefly accomplished by greater or lesser reabsorption in the tubules, and the total amount of glomerular filtrate is altered but little.

**Discussion.** Experimental work on rats and rabbits with one kidney removed shows that compensatory changes may take place in the remaining kidney.<sup>2,3,4,5</sup> These changes often consist of an early opening up of a greater proportion than usual of the glomeruli. Later the renal tissue may increase, owing chiefly to an enlargement of the glomeruli and tubules. Whether or not new glomeruli are formed is disputed.

Hinman<sup>2</sup> has reviewed this subject exhaustively with particular regard to the renal hypertrophy and hyperplasia which may take place in one kidney following damage to the other. Addis, Myers and Oliver<sup>6</sup> found that in the rabbit the urea clearance values were only about 66 per cent of normal 3 to 4 months after nephrectomy, which corresponded closely to the relative weight of the hypertrophied remaining kidney. In dogs, following nephrectomy, there is an immediate depression of function, but the urea excretion is normal in about 11 days.<sup>2</sup> Foster<sup>7</sup> studied 9 patients within 3 weeks after nephrectomy and found the phenolsulphonphthalein excretion normal and the kidney's concentrating ability little if any impaired. In these patients the Addis urea test showed values ranging from 19 to 36, whereas 50.4 is the theoretical normal. Seven of the 9 patients were suffering from renal tuberculosis.

Our results show that following unilateral nephrectomy there may or may not be detectable impairment of renal function.

Immediately following the removal of the kidney the renal reserve in the remaining one is brought into play. In our Cases 1 and 2 it is probable that the increase in function was accomplished partly by greater filtration through the individual glomeruli. Since the tubular reabsorption of fluid was diminished, as indicated by the concentration tests, and since there was no evidence of damage to the tubular cells which could explain this decreased reabsorption, it is probable that it was due to an increased volume of filtrate flowing down each tubule.

The examinations in Cases 1 and 2 carried out 4 to 5 months postoperatively showed no change in function, suggesting that in these particular cases there was little or no actual structural hypertrophy of renal tissue within this period of time. However, subsequent to unilateral kidney removal certain compensatory changes may conceivably take place. Groups 2, 3 and 4 illustrate these changes.

1. There may be functional or structural compensatory changes in both glomeruli and tubules producing a normal renal function. Cases 3 and 4 may be of this type.

2. There may be compensatory changes in the glomeruli, but the tubular compensation is relatively less. Consequently, the total glomerular filtrate is normal in amount but the reabsorbing ability of the tubules is inadequate to provide maximal concentration (Cases 5, 6 and 7).

3. The glomeruli may not undergo compensatory changes and the glomerular filtrate may remain diminished below normal. Under these conditions the tubules can reabsorb water to a high degree and, moreover, they are apparently able to readjust themselves qualitatively so that less urea than normal diffuses back through their walls into the blood. Therefore, although the values found for the creatinin clearance (*i. e.*, filtrate) are somewhat low, the urea clearance values are normal. Cases 8 and 9 belong in this group.

This study also furnishes some information as to the sensitivity of the functional tests employed. In Cases 1 and 2 approximately 30 per cent of the total amount of functioning kidney tissue had been recently removed at operation. Both the creatinin and urea clearance tests showed a reduction of this order of magnitude from the average normal. It would seem not improbable, therefore, that the creatinin clearance test actually gives an absolute and the urea clearance a relative index of glomerular filtration. The values obtained by the urea clearance procedure, however, may be influenced by changes, compensatory or otherwise, which may occur in the tubules. This, however, does not impair the clinical value of the test.

The concentration test does not measure the total amount of functioning tubular tissue, but rather the conditions under which the individual tubules operate. That is, on the one hand, if the quantity or velocity of fluid passing down a normal tubule is increased, it will be unable to concentrate to the usual degree; on the other hand, if the actual tubular structure is altered by disease, an individual tubule may prove incapable of concentrating a normal or even diminished amount of glomerular filtrate. Therefore, an accurate evaluation of the nature of any disturbance in tubular function detected by a concentration test, can be properly attained only by correlation with an estimate of the amount of glomerular filtration.

This study indicates that the renal function of persons with one kidney is completely adequate for their daily needs. The only hazard to such individuals is in the development of complicating disease in the remaining kidney.

**Summary and Conclusions.** 1. The renal function of 12 patients who had undergone unilateral nephrectomy was studied by urea and creatinin clearance, concentration and phenolsulphonphthalein tests. Nine of the patients were quite healthy, 2 had pyonephrosis of the remaining kidney and 1 had hypertension.

2. The 2 cases which were studied immediately after operation

showed diminished values for the clearance and concentration tests. The tests on 7 other uncomplicated cases were normal in 2, and one or more of the tests were slightly abnormal in 5. The 3 patients with complications had marked impairment of renal function.

3. In the absence of complications, the renal function of persons with one kidney is not only adequate, but possesses a reserve capacity as well.

4. The observations confirm the value of urea and creatinin clearance tests in detecting early and quantitative reductions in glomerular function and of the concentration test as a measure of tubular reabsorptive power.

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### NOTES ON THE NATURE OF THE SPLENIC CHARACTERS IN BANTI'S SPLENOHEPATIC ANEMIA AND A METHOD FOR SCORING THEM.

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THE following notes will attempt to assist in the verbal delineation of the spleen in the conditions known as Banti's disease and splenic anemia. The work is a part of the studies attempting to give score values to the diseases of this organ, these notes being particularly devoted to the study of a special group.

The evaluation of changes in the spleen, a sort of scoring system, grew from a request by a surgeon to give figures comparable to those in the method used in the tabulation of tumors, while the part concerning the splenic anemias grew from a remark by an internist that the pathologist could not help in a clinical diagnosis by examination of an excised spleen. Attempts at scoring have met with the difficulty that was foreseen, that of giving a numerical value to a qualitative change. The difficulty of distinguishing between the splenic anemias on the basis of splenic pathology is that there is no clear definition of the clinical terms "splenic anemia" and "Banti's disease."

Studies of this subject fall into the following headings: (1) A description of the tissues from presumably normal and from pathologic organs and the numerical evaluations to be put upon them; this is the basis of a scoring system. (2) The identity of the clinicopathologic states called splenic anemia and Banti's disease. (3) The character of the spleen in the two. (4) The distinctions, if any.

*Technique of Scoring.* The scoring of the spleens was started by preparing a chart to cover every possible alteration in the gross and microscopic anatomy of the organ. This has suffered many modifications and reductions, until finally it was decided that scoring of the gross anatomy was not at all profitable. Numerical evaluation has not led to a final scheme of scoring in figures approaching in definiteness that used for epidermoid carcinoma, which in itself is useful in only a broad and relative manner and by those familiar with it. None the less, a helpful scheme for the micro-anatomy was produced by reducing to the minimum the characters (Table 1) that had to be evaluated, which were found to be 13 in all. Their nature is discussed in the following paragraphs as a basis for these descriptions and enumerations.

TABLE 1.—EXAMPLES OF THE SCORING OF SPLEENS ACCORDING TO THE ARBITRARY MATHEMATICAL SYSTEM AND THE OBSERVATIONS JUST MADE.

	Theoretically normal.	Actual reading normal age 19.	Actual reading normal age 22.	Reading of most complete case of proven Banti's disease.	Reading of almost typical case of splenic anemia, clinically. Traces of case lost.	Score of purpura hemorrhagica.
Follicles . . . . .	2	2	3	1	3	3
Germ centers . . . . .	2	1	1	1	2	3
Pulp . . . . .	2	2	2	1	1	2
Sinuses . . . . .	2	2	3	3	3	3
Sinus endothelium . . . . .	2	2	2	3	2	2
Bloodvessels . . . . .	2	2	2	3	2	2
Bloodvessel wall disease . . . . .	2	2	3	3	2	2
Fibrous tissue . . . . .	2	2	2	3	2	2
Reticulo-endothelial cells . . . . .	2	1	2	3	2	3
Blood . . . . .	2	2	2	1	3	2
Pigment . . . . .	2	2	1	3	2	2
Neutrophils . . . . .	2	2	2	3	2	2
Eosinophils . . . . .	2	2	2	2	1	1
Total . . . . .	26	24	27	30	27	29

Two organs of presumably normal character were fortunately obtained, one from an executed man and one from an accidental death; the men were 22 and 19 years of age, respectively. The characters were given a numerical normal value of 2. If they were reduced in number, smaller in size, they were estimated as 1, whereas, if they were increased, hypertrophic or hyperplastic, they were scored as 3. Allowance in a side chart was made for adventitious changes such as the appearance of myeloid cells, amyloid, abscess, tumors, tubercles and infarcts. These were not scored because they would not be present in any normal spleen.

*Follicles.* The normal follicle is assumed to be a fairly solid collection of lymphoid cells either as a true Malpighian body or as a periarterial spindle. In youth up to 10 years there may be a recognizable "germ center" in a large percentage of follicles. After youth they become progressively fewer and one or two per ordinary section would be within normal limits; if there were none at all they would be registered as reduced.

The normal *follicles* vary from 60 to 100 per sq. cm. of the average microscopic specimen taken just within the subcapsular area. The measurement of their width is so variable that it cannot be quoted even within wide limits. The number of the follicles in enlarged spleens is usually reduced. In none of the spleens of any kind in all this study has there been any evidence of an increase in the number. The number of follicles per sq. cm. in cases diagnosed as Banti's disease has ranged from 9 to 33. The gross bulk of these spleens has been from 2 to  $2\frac{1}{2}$  times the bulk of normal spleens. The bulk of the spleen has been determined by the amount of water displaced. It would, therefore, appear that the reduction of follicles is not due to their disappearance but to their inactivity and their compression by the increased interlying organic mass. Two of the spleens, coming from cases not diagnosed as Banti's disease, had, respectively, 34 and 47 follicles per sq. cm. of a pathologic section and their organic bulk was about twice the normal bulk; the bulk of these two organs was less than that of the spleens from cases satisfactorily diagnosed as Banti's disease. It would appear that those cases that are probably different from the acceptable Banti anemia may have less reduction in the number of follicles as well as less atrophy of the individuals.

The small *splenic lymphocytes* are usually arranged in cords but this systematic and conventional construction is not traceable in all pathologic spleens. These cells must be judged by their apparent abundance or paucity in a given specimen by comparison with an acceptably normal one. In the hemorrhagic purpuras, sometimes in the primary anemias, and in most of the infectious processes, there is an abundance of splenic cells with considerable cytoplasm and a relatively loose nucleus that are to be considered as young or swollen small lymphocytes. Cells corresponding to the youngest or lymphoblast type are only recognizable by special cytologic techniques. Hyperplasia of these elements is to be looked for only in leukemias and some infectious diseases.

*Sinuses.* Under normal conditions the sinuses are usually traceable but are best seen in early hyperemia, both active and passive. One must know in judging a given spleen if it has been incised or perfused. The sinus reticulum is detectable with difficulty and for its demonstration the organ cannot be pressed but should be fixed with the greatest care, whereupon special stains by the silver methods will reveal the delicate filamentous tracery. It is practically absent in chronic splenomegaly, fibrosis beside the sinus overshadowing it in density. Sinus endothelium is flat and obscure in the normal organs but it is prominent in all chronic conditions and in the majority of acute ones also. In the chronic cases it often seems heaped up. The cells comparable to it seem to occur in groups beside the sinuses and sometimes beside the trabeculae. On one occasion a perfect mantle of endothelium was seen around an arteriole, the arrangement suggesting that of endothelioma; this was not in a case of tumor or Gaucher's disease but in a hemolytic anemia. In the early cases of the Banti type there is a moderate prominence of these cells but in the late cases they are not conspicuous.

*Bloodvessels and their walls* in the normal spleen are not particularly prominent but show considerable variation in different parts of the same organ. They should only be readily discernible near trabeculae and in follicles. The walls of vessels are, after adolescence, frequently abnormal;

about one-fifth of the vessels in the two supposedly normal spleens studied showed hyalin change of the media, occasional swelling of the endothelium and unusually wide adventitia.

*Fibrous tissue* in the normal spleen is best understood by the use of a stain like phosphotungstic acid-hematoxylin, the special ones like silver impregnation giving too great a contrast and prominence to the supporting framework. By a good stain it is evident that the fibers are coarser and more numerous than has been usually described. There are two places in which the normal supporting tissue is best examined—around the follicles and just outside the sinuses.

The lower degrees of fibrous tissue increase are difficult to decide upon; more advanced grades are relatively easy. Apparent or relative decrease in fibrous tissue is perceptible in the acute "splenic tumors" such as occur in septicemia and typhoid and in the chronic swellings of the purpuric and hemolytic types. It is in both instances almost certainly relative, there being no reason to assume that true destruction occurs.

*Reticulo-endothelial cells* are usually plainly visible in the two forms that may be recognized for the spleen—the large mononuclear lying in a lacuna of the pulp and the medium sized mononuclear lying between the sinuses and lymphoid groups. Their increase is perceptible, and largely confined to the medium sized mononuclears, there being increase of giant mononuclears only in the lipoidic spleens. A decrease in the mononuclears is probably relative and only to be expected when their place is taken by blood, fibrous tissue and lymphocytes. Sometimes these cells are distinctly phagocytic, but in the absence of marked pigmentation, phagocytosis is not a prominent feature of splenic pathology; the malarial and hemolytic anemias are exceptions.

The presence of *blood* within vessels and sinuses and diffusely within the splenic tissue is readily perceived, but its amount depends upon the method of the removal of the spleen and its treatment afterward. In the more acute cases of the hepatosplenic anemias the blood is found uncoagulated and agglutinated; in some of the later cases both of these features may be found.

*Pigment* under normal conditions is sparse in the spleen and yet, in the two probably normal spleens studied, several small groups were found lying free and one large group was found in a giant mononuclear.

*Neutrophils* scattered singly throughout the tissue are much more common than is generally supposed; this is also true of the eosinophils. Under conditions of acute infection, hemolytic anemias, Hodgkin's disease, tuberculosis and the like, both of these types may be found increased. In 18 cases of the Banti type that we have examined especially for this cell, they have exceeded normal 4 times. Eosinophils are, however, definitely less readily found than are the neutrophils, but occasionally they may be quite prominent. They seem to be more common in the younger cases than in the older ones of chronic splenomegaly, and are very conspicuous on account of their redness.

Splenic anemia may be defined, according to the writings of Osler (1902), Stengel (1904) and Rolleston (1914), as a chronic anemia with splenomegaly (which is often the first change), of unknown cause, with a blood picture with a low color index, a reduction of red cells possibly hemolytic in origin, leukopenia or normal white count, moderate reduction of thrombocytes, no lymph gland enlargement, liability to gastro-intestinal hemorrhages and with an illness naively stated by Rolleston as "prolonged with a tendency to spontaneous cure and with splenectomy curative, if successful."

Banti's disease is like this, but passes into a stage in which cirrhosis of the liver is the prominent pathologic feature and which is combined with jaundice, ascites, further anemia and fatal end. According to Rolleston, Banti's disease occurs more in females and below full middle age; he suggests that the reverse is true in splenic anemia.

Briefly then, the distinction from a clinical standpoint is that in splenic anemia there is no hepatic disease, whereas when cirrhosis and ascites appear it should be called Banti's disease. MacCarty in his analysis states, "For practical purposes the two diseases are usually considered as one."

It might be profitable to devote a few lines to indicate how these words came into use and make mention of a recent discussion on the subject. Stengel credits the origin of the term splenic anemia to W. Griesinger in the middle of the 19th century, but adds that Banti emphasized the term in 1884. Banti himself states that Gretzel (a pupil of Griesinger) in 1866 first made use of the name.

The Italian author described a disease of three stages, insidious and of long duration, many years indeed, consisting of anemia and enlarged spleen, a quiescent period of variable length and a terminal stage of hepatic cirrhosis and ascites. He recognized the similarity of this disease and splenic anemia but insisted that they were different because of the duration, course and hepatic change. Senator, 1901, noted that to the symptom complex described by Banti, gastro-intestinal hemorrhages and local escape of blood might be added. He thought that hepatic cirrhosis need not cause the ascites which could be due to venous obstruction by the large spleen.

Disease of the walls of the splenic artery and vein have been mentioned several times in the literature and thought to be the cause of the splenohepatic disease. Certain other diseases, such as Gaucher's disease and tuberculosis of the spleen, were formerly confused with the conditions under discussion.

Rolleston, commenting on these diseases, makes the point that the stages need not be so protracted as Banti would have it and may indeed so run together that no sharp limits can be detected. He states that there are certainly cases corresponding to the description of Banti but that they appear to be more in the ward than on the autopsy table.

At the meeting of the Association of American Physicians, May, 1932, a discussion took place under the stimulation of a report by Howard and Mills, whose work credited the existence of a clinico-pathologic state that corresponds to Banti's disease, yet over half of their cases failed to show hepatic changes. Dr. Howard thinks that only a limited number of cases should rightly be called Banti's disease, but that such undoubtedly exist.

Possibly some of the following considerations will help to decide whether these two terms are justifiable. The condition has not much improved since the very pertinent words of Stengel, 1904,

when he states: "It would be hopeless in the present state of knowledge to attempt a classification of all of the cases that have been reported. On the other hand, it is very evident that there are very different sorts of cases that have more or less superficial resemblance, and I cannot share the view that all are probably instances of one disease in different stages."

Judging from 13 fresh spleens that have been examined grossly and in which clinical diagnoses were acceptable, the features were so nearly constant without regard to diagnosis that they may be described together. Whether or not there are several diseases represented, the gross appearance of the organ does not help to solve the matter. To these have been added the records of 10 other cases and all 23 have been studied microscopically.

**The Spleen.** It weighs from 600 to 1600 gm. The general shape is preserved, the notch being usually perceptible. The general splenic outline falls within normal variations; the capsule is slightly thickened, smooth, regular, translucent. There may be patches of local chronic perisplenitis, which are best ascribed to reaction to local trauma or to inflammation in the vicinity; there is no reason to believe that perisplenitis would arise from endosplenitis. The cross section is usually dark brown, firm, rather homogeneous in appearance with a perceptible increase in delicate red-gray strands that correspond to a multiplicity of fine trabeculae. Faint red-gray dots may suggest the Malpighian bodies but a prominence of such markings has not been recorded.

It has been one of the outstanding pathologic and etiologic features of the pathologic anatomy of the spleen and liver in these conditions to emphasize the existence or possibility of sclerosis of the splenic vein and of the gastro-splenic artery. In 1 case, of the series here discussed, there were found endophlebitis and obliterative endarteritis between the liver and spleen, and in 1 case a sclerosing and calcifying phlebitis. The condition of the splenic vein should be noted with greater exactness by both surgeons and pathologists.

*The microanatomy of the spleen* in the cases of the present study is now taken up in order of the features that we have found important.

The capsule is slightly thickened, and beneath it there is no loose space that could pass for a marginal sinus, the pulp tissue growing up directly to the fibrous coat.

The follicles are diminished in number and size. The "germ centers" are for the most part somewhat below normal limits of size and number, although there are many instances in which they may be plainly seen. Where they are seen there is a hyalin change in the interstitial fibers, or the entire central zone of the follicle may be a hyalin mass with a cell or two and usually without recognizable bloodvessels. This hyalin mass may at times contain many silver-staining fibrils.



It has already been emphasized that the number and size of the follicles should be estimated in terms of the size of the whole spleen. This relative value assists very materially in estimating their increase or decrease—an item again mentioned in discussing two spleens that vary in microscopy from the Banti picture.

The pulp is usually poor in small lymphocytes and, with rare exceptions, never contains what would be called an excess thereof.

The sinuses are for the most part dilated. The sinus endothelium is usually inconspicuous. It may seem atrophic and there is rarely, if ever, a desquamation of endotheliocytes. Care must be taken in interpreting this, because in many studies spleens are perfused while many others are opened and allowed to drain and collapse. When the organ is removed by operation the hemostats or clamps should be allowed to remain on the vessels of the stalk until the pathologist has opportunity to perfuse the spleen or cut it immediately before it is put into fixative. About one-third of our specimens were perfused. The irregularity of the chance to carry out this technique has made it almost an impossibility to compare organs removed during early stages *versus* those from cases of longer duration.

The bloodvessels are within normal limits of number. The arterioles of follicular centers, of the edge of trabeculae and the occasional one in the pulp, show slightly more disease in the wall than they would in a presumably normal spleen of comparable age; this is true irrespective of the duration of the disease.

The veins of trabeculae are usually distended. There is often a hydropic change in the media and on two occasions there were early calcium deposits. Marked pathologic change in these veins is, however, not an outstanding feature.

Fibrous tissue is everywhere increased. In the cases in which the spleen has been removed less than 1 year from the inception of symptoms, the fibrous tissue increase is almost as easily recognized as in cases existing much longer than this. Occasionally a deeply stained band, shown by Van Gieson or silver methods, may completely surround a follicle. The perivascular fibers are prominent. The trabeculae seem to spread out as numerous delicate, yet intricately wound and mixed silver-staining fibers; some of the strands running through the pulp may be massed and hyalin.

Reticulo-endothelial cells appear to take the usual two forms. The large single mononuclear giant cell is not increased; the moderate sized mononuclear, resembling an endotheliocyte, is definitely increased. The endotheliocyte is plainest in spleens that have been removed about 1 year after inception. They lie along the sinuses, sometimes in veins and occasionally in a row along the connective tissue strands. It does not seem possible that their number contributes very greatly to the increased size of the organ.

The amount of blood in the organ, as judged by the microscopic

appearance, is quite variable. It gives a slightly lower score value in spleens removed within 3 full years since the first symptom, and more in organs removed in later years. This observation is not in accord with those on specimens studied by the writer some years ago, coming from supposed Banti's disease of less than a year's duration, that were found to contain much more blood, while another case of long standing was quite poor in free blood. Aschoff and McCallum think that the earlier stage is accompanied by excessive bloodiness. However, not all cases progress at the same rate, and not all spleens have been handled for examination in the same manner.

Pigment is slightly increased and varies directly with the amount of blood perceptible in the sections.

Neutrophils, eosinophils and plasma cells appear to be of no significance. Other recognizable marrow elements are not recorded.

There are 2 cases in the 23 specimens in which the follicles stand out as different from the others and in several ways there are slight variations from the picture just given. These 2 cases deserve a little attention.

The follicles in these cases were all larger than the average of the 2 presumably normal organs and of 34 routine spleens from autopsy material. In these 2 the "germ centers" were apparently more prominent. In both cases the bloodvessels were more numerous. The reticulo-endothelial cells were less conspicuous, the blood within normal limits, the pigment perhaps slightly increased. These cases, respectively 4 and 22 years old, both had their spleens removed after at least 1 year of illness (one 5, the other unknown). The distinction of these two spleens from the others is more readily apparent to the eye than from the written description. They have been diagnosed as splenic anemia, an apparently justifiable distinction in at least one of them, since there was neither jaundice nor ascites, and 3 years have passed after splenectomy without the appearance of ascites.

The liver in the 23 cases has been changed clinically in 10 of 16 instances where it is mentioned, and actually changed, as seen at operation or autopsy, in 7 out of 14 in which it is mentioned. Jaundice was present in 3 out of 14 cases, of which the history records dependable observations. Ascites was present in 6 out of 20 cases and corresponded with definitely known change of the liver 4 times out of the 6. Of the 23 cases, 6 died following splenectomy, 8 are reported living 3 to 8 years and all are invalided. Six of these 8 are recorded as having had postoperation hemorrhages.

**Discussion.** A distinction of the types of spleens and a clear separation of all these cases into splenic anemia on one hand and Banti's disease on the other seems at present very difficult. The clinical evidence at hand supports strongly the thought that there is a probability of liver damage in most cases of chronic spleno-

megaly. Only 2 of 14 traceable cases seem to have passed 2 years without clinical or definite pathologic information that the liver was involved. The evidence would support the idea that there is a condition of Banti's disease, the early stages of which are splenomegaly with anemia. The late stages are chiefly hepatic with jaundice and ascites. The name Banti's splenohepatic anemia is suggested. Those that do not fall into this group, ably covered by Stengel,<sup>4</sup> remain yet to be classified and the term splenic anemia would better be restricted to description and discussion.

The spleen of Banti's splenohepatic anemia can be described as an enlarged organ, without characteristic capsular change, with reduction in the size and relative number of follicles, fibrosis of follicular centers, of pulp and of trabecular lines, a prominence of mononuclears, a relative atrophy of the pulp, and a variation of blood and pigment depending upon the duration of the enlargement. It is distinct from the enlargement due to primary hepatic cirrhosis which has marked congestion, pigmentation, prominence of lymphoid structures and limited fibrosis. It is distinct from the hemorrhagic purpuras and anemias which have much blood and pigment, a prominence of endothelial cells and phagocytes, and a relative paucity of silver-staining fibers. It is distinct from malarial spleens because the latter show pigmentation, a fine fibrosis, diffuse lymphoid hyperplasia with much phagocytosis. It differs from the syphilitic and tuberculous spleens by the absence of distinct inflammatory foci. With these one finds a combination of marked sinus catarrh, plasma cells and eosinophils; masses of endotheliocytes may be present in these spleens. It is separated from Hodgkin's disease of the acute type by the presence in the latter of large zones of endotheliocytes, giant cells, eosinophils and polymorphonuclears, and from the chronic type with less ease because of the irregular fibrosis of this form.

It would seem from this survey that a strict scoring of the splenic characters will not lead to a numerical value that can be definitely identified with these specific clinical or pathologic entities. By familiarity with this method, or one like it, it may be possible to obtain distinct leads as to the part of the organ that is giving the most definite reaction.

The characters discovered do not permit a sharp separation of the spleens that come from cases called Banti's disease and those called splenic anemia. Many chronic splenic anemias are associated with hepatic disease comparable to that described by Banti. The clinical terms are not used with critical care. It cannot be stated that any considerable number of the cases with splenomegaly and anemia, in which splenectomy was done, may not have terminated with hepatic disease. These studies include one complete record of Banti's disease diagnosed before splenectomy, when there was nothing to suggest hepatic disease by observation at laparotomy,

that died from pneumonia 2 years later and showed a cirrhosis and ascites.

Therefore, it seems acceptable to use the term "splenohepatic anemia" or "Banti's disease" and to omit the clinical diagnosis of splenic anemia, employing instead "anemia with splenomegaly." There may be cases in the melange of the obscure anemias that have simply enlargement of the spleen, anemia and gastro-intestinal congestion that will not go on to hepatic pathology. They are probably rare and further study may identify them.

The characters of the spleen in Banti's disease will help to make the clinical diagnosis and are to be summed up as diminution in the size and relative number of follicles per square area; an increase of fibrosis around follicles, along sinuses and in the neighborhood of trabeculae, and a prominence of many fine trabeculae; a hyalin accumulation in the center of follicles, a prominence but no great exaggeration of large mononuclears, and a slight increase of pigment.

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## DETERMINATION OF NON-PATERNITY BY MEANS OF BLOOD GROUPS.

### WITH SPECIAL REFERENCE TO THE AGGLUTINOGENS M AND N OF LANDSTEINER AND LEVINE.

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IN our country the possible application of blood grouping in medicolegal cases for the determination of non-paternity has not received the recognition that it has received in many European countries. So reliable is the application of blood grouping for this purpose, that in 1929 Schiff<sup>1</sup> succeeded in collecting 5584 cases in which blood groups had been so applied in Germany, Austria, Denmark, Sweden and Switzerland. Since 1929 this method has also been adopted in Russia, Norway, Japan, the Netherlands, Italy, and Great Britain.

That human bloods can be subdivided into definite groups, because of the ability of the serum of one normal individual to agglutinate the red blood cells of certain other human beings, was first recognized by Landsteiner in 1900.<sup>2</sup> Landsteiner explained this phenomenon by postulating the existence of two isoagglutinogens, A and B, in the red blood cells, and of two isoagglutinins,  $\alpha$  and  $\beta$ , in the blood serum, such that  $\alpha$  is specific for A, and  $\beta$  is specific for B.<sup>3</sup> In Table 1 is shown the difference in composition of the 4 Landsteiner blood groups, together with the old numberings of Moss and Jansky, and the international nomenclature officially recognized by the Health Committee of the League of Nations. The old nomenclatures, no longer used in scientific publications, are only given here because they are still being used in some of our hospitals. The existence of two systems of numbering has resulted in confusion on many occasions, and has also been responsible for several transfusion accidents. Since the international nomenclature depends upon the agglutinin content of the red blood cells, it can cause no confusion.

TABLE 1.—CLASSIFICATION AND COMPOSITION OF THE LANDSTEINER BLOOD GROUPS.

Jansky.	Moss.	International.	Cells (agglutinin).	Serum (agglutinin).
I	IV	O	—	$\alpha$ and $\beta$
II	II	A	A	$\beta$
III	III	B	B	$\alpha$
IV	I	AB	A and B	—

In 1908, Epstein and Ottenberg presented the first data on the heredity of blood groups.<sup>4</sup> In 1910, von Dungern and Hirschfeld<sup>5</sup> showed that the agglutinogens A and B are inherited as Mendelian dominants; and in 1924, Bernstein<sup>6</sup> demonstrated that the heredity of the agglutinogens A and B depends upon three allelomorphie genes, A, B and R, where A and B are dominant, and R is recessive. Therefore, the 4 blood groups may be subdivided into genotypes as follows: Group O, genotype RR; Group A, genotypes AA and AR; Group B, genotypes BB and BR; and Group AB, genotype AB. The heredity of the Landsteiner blood groups, according to the Bernstein theory, is shown in Table 2.

TABLE 2.—HEREDITY OF THE LANDSTEINER BLOOD GROUPS.

Groups of parents.	Groups of children possible.	Groups of children not possible.
O $\times$ O	O	A, B, AB
O $\times$ A	O, A	B, AB
O $\times$ B	O, B	A, AB
A $\times$ A	O, A	B, AB
A $\times$ B	O, A, B, AB	
B $\times$ B	O, B	A, AB
O $\times$ AB	A, B	O, AB
A $\times$ AB	A, B, AB	O
B $\times$ AB	A, B, AB	O
AB $\times$ AB	A, B, AB	O

How the blood groups can be applied in an actual paternity case is illustrated in the following two hypothetical examples: A man charged with the paternity of a child denies ever having had intercourse with the plaintiff, so the blood groups of man, woman and child are determined. The man is found to belong to Group A, the woman to Group A, and the child to Group B (see mating 4 of Table 2). Since the mother does not possess agglutinin B, but the child does, this agglutinin must have come from the father, who could therefore only belong to Group B or Group AB. The blood groups in this case, therefore, have furnished absolute proof of the man's innocence. Let us suppose, on the other hand, that in another similar case the blood groups were as follows: man, Group B; woman, Group A; and child, Group AB. As may be seen from Table 2 (see mating 5), such a combination of groups is entirely possible. This, however, is no proof that the man charged with paternity is the true father; for in a population such as that present in this country, about 15 per cent of all individuals belong to Group B. The man in question is no more proved to be the father than is any other man belonging to the same group. Blood groups, therefore, are of no value as an aid to proving paternity; they can only be used to prove non-paternity.

In not every case where a man is unjustly accused of paternity is it possible to exclude him as a father of the child. Thus, if the putative father and the true father both belong to the same group, no exclusion will be possible. It has been calculated that the average chances of proving non-paternity by means of the Landsteiner blood groups are approximately 1 in 6.<sup>7,8</sup>

The chances of proving non-paternity have been doubled by the discovery by Landsteiner and Levine of several additional agglutinogens in human red blood cells.<sup>9</sup> Two of these, termed M and N, respectively, were studied in great detail, and Landsteiner and Levine demonstrated that they are inherited as Mendelian dominants.<sup>10</sup> According to their theory, the heredity of these agglutinogens depends upon a single pair of allelomorphic genes, M and N. There are therefore only three genotypes possible: MM, MN, and NN; corresponding to the three phenotypes: M+N- (blood possessing agglutinin M, but lacking agglutinin N), M+N+ (blood possessing both agglutinogens, M and N), and M-N+ (blood possessing only agglutinin N). According to the theory, therefore, bloods of type M-N- (lacking both agglutinogens) are impossible. As a matter of fact, although almost 20,000 specimens of blood have been examined to date by Landsteiner and Levine, Schiff,<sup>11,12</sup> Wiener, *et al.*,<sup>13,14,15</sup> Thomsen,<sup>16</sup> and Clausen,<sup>17</sup> not a single blood lacking both agglutinogens has been found to date. The present author has personally examined more than 3000 specimens of blood without finding a single exception to this law. This, certainly, is impressive confirmatory evidence of the theory of Landsteiner and Levine.

The heredity of the agglutinogens M and N is very easily derived from the theory, as shown in Tables 3 and 4. Thus, in the  $M+N- \times M+N-$  mating, the genotype of both parents is MM. The gametes (sperm and ova) each contain the single gene M, so that all the zygotes must be of genotype MM. All the children of such a mating must therefore be of type  $M+N-$ . Similarly, in the  $M+N- \times M+N+$  mating, the genotypes of the parents are MM and MN, respectively. The former parent can only produce gametes containing gene M, the latter parent produces gametes with gene M and gametes with gene N in equal numbers. Half of the zygotes must therefore be of genotype MM and half of genotype MN, corresponding to the phenotypes  $M+N-$  and  $M+N+$ , respectively. The other four matings in Table 3 were worked out in a similar manner.

TABLE 3.—HEREDITY OF AGGLUTINOGENS M AND N.

Cross.	Per cent children of types.		
	$M+N+$	$M+N-$	$M-N+$
$M+N+ \times M+N+$	50	25	25
$M+N+ \times M-N+$	50	0	50
$M+N+ \times M+N-$	50	50	0
$M+N- \times M-N+$	100	0	0
$M+N- \times M+N-$	0	100	0
$M-N+ \times M-N+$	0	0	100

TABLE 4.—MEDICOLEGAL APPLICATION OF THE AGGLUTINOGENS M AND N.

Types of parents.	Types of children possible.	Types of children not possible.
$M+N+ \times M+N+$	$M+N+$ , $M+N-$ , $M-N+$	
$M+N+ \times M-N+$	$M+N+$ , $M-N+$	$M+N-$
$M+N+ \times M+N-$	$M+N+$ , $M+N-$	$M-N+$
$M+N- \times M-N+$	$M+N+$	$M+N-$ , $M-N+$
$M+N- \times M+N-$	$M+N-$	$M+N+$ , $M-N+$
$M-N+ \times M-N+$	$M-N+$	$M+N+$ , $M+N-$

**Technique.** The technique of testing for the agglutinogens M and N is much more complicated than the technique of testing for A and B. There are no natural agglutinins for M and N; the testing sera are obtained by immunizing rabbits. To produce anti-M serum, blood of type  $M+N-$  should be used; to produce anti-N serum, blood of type  $M-N+$  is used. The blood selected should also belong to Group O, so that no agglutinins are formed against A and B. The technique I have found most effective is to alternate courses of daily intravenous injections with long rest periods. If 12 rabbits are to be immunized, 25 cc. of blood will suffice for one course. The blood should be divided among 7 or more tubes (for a course of 7 days or longer), containing the following solutions, recommended by Rous and Turner<sup>18</sup> for preserving blood: 5.4 per cent glucose (5 parts); 3.8 per cent sodium citrate (2 parts); whole blood (3 parts).

The solutions must be sterile, and the blood must be collected under sterile precautions. When stored in the ice box in this manner, blood may be kept for several weeks. Before injecting the blood into the rabbits, the contents of each tube should be washed with sterile saline and then diluted up to a convenient volume. The washed blood is then divided equally among the 12 rabbits. All the injections of the first course are given intravenously. The first injection of each of the subsequent courses is given

intraperitoneally (to avoid anaphylaxis); all other injections are given intravenously. The rest periods between courses should be about 7 to 10 days. The rabbits are bled and the sera examined for their agglutinin content 1 week after the last injection. After 3 or 4 courses of injections, most rabbits will produce good anti-N sera. It is much more difficult to produce anti-M sera, however. We finally succeeded in producing a very potent anti-M serum, by giving 2 rabbits which had had several courses of injections, followed by a rest period of *several months*, 1 additional course of injections. When preparing these sera it is wise to start with a large series of rabbits, since because of the protracted nature of the immunization (particularly for M), most of the rabbits will die before the experiment is completed.

To test the sera a few cubic centimeters of blood are collected from an ear vein and then allowed to clot. The serum is separated off by centrifuging, and then inactivated by heating to 56° C. for half an hour. This serum not only contains agglutinins against M (if the rabbit was immunized with M+N- blood) or N (if the rabbit was immunized with M-N+ blood), but also species agglutinins acting on all human blood. A potent serum will agglutinate any human blood at a titer of 1 to 3000. To prepare the testing fluid from the serum, the species agglutinin must be removed by absorption. We prepared our anti-M fluid from serum M 905. This serum was diluted 50 times and mixed with half a volume of packed, washed cells of type M-N+. After standing for 30 minutes at room temperature, the mixture was centrifuged at high speed. The supernatant fluid now only contained agglutinins against the factor M. Our N fluid was prepared from the serum of rabbit N 2. This serum was diluted 20 times and absorbed with half volume of packed, washed cells of type M+N- at 37° C. The testing fluids thus prepared were stored in the ice box after the addition of 1 drop of toluol per cubic centimeter of fluid. (The use of this preservative was suggested to us by Dr. Philip Levine. The addition of toluol preserves the testing fluid for more than 6 months. Without toluol, on the other hand, the testing fluid deteriorates rapidly and usually must be discarded after a few weeks.) Before use, the M fluid was further diluted three times (making a final dilution of 1 to 150), and the N fluid two times (a final dilution of 1 to 40).

The blood to be tested is suspended in saline and citrate, washed once and resuspended in normal saline solution to make a 2.5 per cent suspension. One drop of the cell suspension, 2 drops of saline, and 1 drop of testing fluid are mixed in a small test tube, the mixture is then centrifuged for 5 minutes at 1800 r.p.m. After centrifuging, the tubes are replaced in the rack, which is then shaken until the negative control has broken up into an even suspension. (Control bloods of all three types must be included in every experiment.) The reactions for M are always easy to read. There will be occasional difficulty with the N reactions, however, but whenever this occurs the difficulty will resolve itself if several different N fluids are used, and if the tests are repeated a sufficient number of times.

We did not find it necessary to use any preservative for the concentrated immune rabbit serum. After the preliminary tests had been performed, the rabbits which had been found to have potent sera were bled from their marginal ear vein, which was cut after the ear had been previously rubbed with a small amount of xylol. In this manner, as much as 40 cc. of blood could be obtained, and at the same time the rabbit could be kept alive for further experimentation. The blood was allowed to drip into sterile 10 cc. tubes, and after the blood had stood overnight in the ice box the serum was separated by centrifugation. The serum was then transferred to sterile 1 cc. vials by means of sterile pipettes. The vials were hermetically sealed, and the serum was then stored in the ice box. Serum so kept was



found to show no appreciable diminution in titer after two years, provided that there was no contamination. The serum that is to be stored need not be inactivated, since it loses its complement after standing for several days in the ice box.

Though members of our laboratory staff have been repeatedly examined for M and N during the past 3 years, in no case has a change in type been noted.

In Table 5 we have summarized the results obtained up to date on the heredity of the agglutinogens M and N. These data, which include 674 families with 1899 children, present 8 "exceptions" to the theory of Landsteiner and Levine. That these "exceptions" are undoubtedly due to illegitimacy will now be proven.

TABLE 5.—SUMMARY OF ALL DATA ON THE HEREDITY OF THE AGGLUTINOGENS M AND N.

Types of parents.	Types of children.			Totals.
	M+N+	M+N-	M-N+	
M+N+ × M+N+ . . . . .	256	113	93	462
M+N+ × M-N+ . . . . .	218	2	225	445
M+N+ × M+N- . . . . .	305	260	3	568
M+N- × M-N+ . . . . .	181	0	2	183
M+N- × M+N- . . . . .	1	157	0	158
M-N+ × M-N+ . . . . .	0	0	83	83
Totals . . . . .	961	532	406	1899

This table includes:

64 families with 286 children by Landsteiner and Levine.<sup>10</sup>

131 families with 642 children by Wiener and Vaisberg.<sup>13</sup>

72 families with 192 children by Schiff.<sup>12</sup>

290 families with 577 children by Clausen,<sup>17</sup> of which

102 families with 105 children had been previously reported with Thomsen<sup>16</sup> and

117 families with 202 children by Lattes and Garrasi.<sup>20</sup>

For medicolegal purposes the mechanism of heredity of the agglutinogens M and N may be summarized in two laws:

1. The agglutinogens M and N can never appear in the blood of a child unless present in the blood of one or both parents.

2. The combinations M+N- parent with M-N+ child, and M-N+ parent with M+N- child are impossible.

TABLE 6.—SUMMARY OF ALL MOTHER-CHILD COMBINATIONS.

Authors.	Number of mothers.	Number of children.
Landsteiner and Levine (families) . . . . .	64	286
Wiener and Vaisberg (families) . . . . .	131	642
Schiff (families) . . . . .	72	192
Clausen and Thomsen (families) . . . . .	290	577
Lattes and Garrasi (families) . . . . .	117	202
Schiff (forensic cases) . . . . .	..	525
Schiff (newborn) . . . . .	..	566
Wiener, Rothberg and Fox . . . . .	461	497
Totals . . . . .	..	3487

A rigid test of the theory may be made by examining a large series of mothers and their children (to eliminate the possibility of illegitimacy), in order to determine whether or not exceptions to

the second law ever occur. In Table 6, therefore, we have summarized all the mother-child combinations that have been studied thus far. *In this series of 3487 cases, not a single exception to the theory of Landsteiner and Levine was found.* This proves conclusively that it is impossible for an  $M+N-$  mother to have an  $M-N+$  child, or *vice versa*. Since the agglutinogens M and N are independent of sex in their heredity, the same statement must also hold for the father. Exceptions to the second law in family studies that implicate the father must therefore be due to illegitimacy.

If we now analyze the 8 "exceptions" in Table 5, we find that 7 of them are "exceptions" to the second law implicating the father, and therefore must be due to illegitimacy, as the authors themselves believed. The eighth case, which was found by Wiener and Vaisberg, is an "exception" to the first law, and is also undoubtedly due to illegitimacy, since such exceptions due to illegitimacy are rather to be expected in studies on a large series of families.

Landsteiner and Levine, and Wiener and Vaisberg also examined their families for the Landsteiner blood groups. Landsteiner and Levine found 6 "exceptions" to the heredity of the 4 blood groups due to illegitimacy, whereas Wiener and Vaisberg found only 1, indicating that the morals of the people studied by the former authors were lower. Therefore, the fact that Landsteiner and Levine found 5 of the 8 "exceptions" of Table 5, whereas Wiener and Vaisberg found only 2, corresponds to the expectations.

On the basis of this large series of studies, the medicolegal application of the agglutinogens M and N for the determination of non-paternity is fully justified at present, together with the application of the classic blood groups. By the combined use of all 4 agglutinogens, A, B, M, and N, it is possible to exonerate one-third of all men falsely accused of paternity.

To illustrate the method of application, and also because blood groups have been so little applied in this country for the determination of nonpaternity, I shall quote my experiences in 5 cases:

**Case Abstracts.** CASE 1 (previously reported<sup>19</sup>).—The question arose in this case whether the husband or another man was the father of a child. The husband was willing to support the child regardless of its paternity, but the wife insisted that she would only live with the child's true father. Dr. A. A. Eggston grouped the bloods of all 4 individuals, but as both men belonged to Group A, no decision could be rendered. He therefore referred the case to me for the application of the agglutinogens M and N. By this method, the lover could be definitely excluded as possible father of the child, since he belonged to type  $M-N+$ , whereas the child belonged to type  $M+N-$ . Of the two men, therefore, the husband could only have been the true father. The complete results of the blood examinations were:

Blood of:	Group.	Type.
Husband . . . . .	A	$M+N-$
Lover . . . . .	A	$M-N+$
Wife . . . . .	B	$M+N-$
Child . . . . .	A	$M+N-$

It is an interesting illustration of human nature that the woman finally left her husband for the lover regardless of the paternity of the child.

CASE 2.—This case was referred to me by Dr. S. H. Polayes, since he could render no decision by means of the classic Landsteiner blood groups. In this case, a man who had relations with his wife before marriage, and who had married her when she told him she was about to give birth to a child, desired a divorce, and as an excuse claimed that the child (at the time 2 years old) was not his. The findings were:

Blood of:	Group.	Type.
Husband . . . . .	A	M+N—
Wife . . . . .	A	M+N+
Child . . . . .	O	M+N+

Since such a combination of groups is entirely possible, it is impossible to determine whether or not the child is legitimate.

CASE 3.—In this case a woman charged a man with the paternity of her child. Although the man admitted having had relations with the woman, he claimed that other men had had relations with her at about the same time. The court ordered blood tests, and the bloods were shipped to me from New Haven. The results were:

Blood of:	Group.	Type.
Putative father . . . . .	A	M—N+
Mother . . . . .	O	M+N+
Child . . . . .	O	M—N+

Here again it is impossible to tell whether or not the man is the father of the child.

This case is important, however, because it illustrates how these tests can be introduced into our courts, provided that the lawyers and judges are progressive enough. The judge who ordered the blood tests for this case (New Haven Court of Common Pleas) stated that this was a new question to him, but if the tests resulted so that the examining physician, upon proper qualification, could state that the defendant could not have been the father, it would be important evidence. The results of the tests in this case left the question open, but upon other evidence, the defendant was adjudged the father of the child.

CASE 4.—This case was referred to me by Dr. W. G. Flickinger. Because he had suspected his wife of infidelity for a period of years, a man desired to have blood tests performed on his wife, his 2-year-old son, and himself. He also had a 14-year-old daughter of whose legitimacy he felt certain. The results were:

Blood of:	Group.	Type.
Husband . . . . .	A	M+N—
Wife . . . . .	O	M+N—
Son . . . . .	O	M+N—

Here again no decision could be rendered.

CASE 5.—After 8 years of married life, during which time she had had frequent intercourse with her husband but had failed to become pregnant, Mrs. X met and fell in love with Mr. Y. Soon thereafter a boy was born, and 3 years later a girl was born. At about this time Mr. X discovered the relations between his wife and Mr. Y. When Mrs. X expressed her desire to leave her husband for Mr. Y, Mr. X threatened to take the case to court, where the custody of the children would most probably be awarded to him. Mrs. X felt that the children were Mr. Y's, and finally persuaded her husband to have blood tests performed. It was found at that time

that the husband, wife, and two children all belonged to group O, and that the lover belonged to Group A, so that no decision was possible. Two months ago a third child was born, a girl; the boy now being 5 years old, and the second child 2 years of age. In order to effect a final solution of their problem, these people came to New York for complete blood tests. The results were as follows:

Blood of:	Group.	Type.
Husband . . . . .	O	M + N +
Lover . . . . .	A	M - N +
Wife . . . . .	O	M + N +
First child . . . . .	O	M + N +
Second child . . . . .	O	M + N -
Third child . . . . .	A	M - N +

It can readily be seen that the lover could not be the father of the second child; and that the husband could not be the father of the third child. No decision is possible concerning the first child. In this case, therefore, our blood tests have succeeded in determining the paternity of 2 out of 3 children; for we have indirectly proved that the second child was the husband's and the third child was the lover's.

CASE 6.—In this case (New Haven Court of Common Pleas) the use of blood-grouping prevented a miscarriage of justice. E. N. charged L. R. with the paternity of her child, and after a preliminary hearing L. R. was held for trial. Although the defendant repeatedly denied his guilt, the weight of public opinion was against him. The attorney for the defendant suggested blood-grouping tests, to which the man, woman and child were subjected. The results of the tests were as follows:

Blood of:	Group.	Type.
Putative father . . . . .	A	M + N +
Mother . . . . .	O	M + N +
Child . . . . .	B	M + N -

Since a Group O mother cannot give rise to a Group B child unless the father belongs to Group B or Group AB, L. R., who belongs to Group A, could not be the father of the child. After conferring with her lawyer, E. N. decided to withdraw her charges, and judgment was rendered for the defendant.

It seems hardly necessary to emphasize the importance of employing the utmost care when applying blood grouping for medicolegal purposes, since errors in technique can only serve to discredit all this work, as well as bringing about grave injustice. When testing for the Landsteiner blood groups, errors are practically impossible if both cells and serum of each blood are examined (see Table 1). Several potent testing sera of each group should be used, and several control bloods of each group should be included in every experiment. The tests should also be performed upon two independent samples of blood.

With respect to the examination of the bloods for the agglutinogens M and N, as we have already pointed out, the technique is somewhat more involved than the technique of typing for the classic blood groups. It is therefore of the utmost importance that the tests in medicolegal cases be performed by experts, *i. e.*, individuals who have done a considerable amount of work in this field and particularly with the agglutinogens M and N.

**Summary.** The medicolegal application of the Landsteiner blood groups for the determination of non-paternity is urged on the basis of the experiences of European countries during the past 10 years. The application of the *probandi* groups M and N of Landsteiner and Levine is also fully substantiated, on the basis of studies on families totaling more than 3000 children. The method of application is illustrated by actual experiences in 6 cases, in 3 of which valuable information was obtained.

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## A CHEMICAL PECULIARITY OF PELLAGRA BLOOD (RAPID IODIN DECOLORIZATION).

### PRELIMINARY NOTE.

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IN diseases with protean symptoms alterations of the blood are frequent and are often sufficiently well marked to be of diagnostic value. Goldberger<sup>1</sup> has emphasized that many cases of pellagra are overlooked owing to the limitation of their symptoms, in contrast to the manifestations of the well-developed classical case.

To quote, "While there is danger that conditions not pellagrous may be diagnosed as pellagra, there is perhaps greater danger that pellagra will fail of recognition. It is important to keep in mind the possibility of pellagra in cases of 'neurasthenia,' 'melancholia,' 'chronic indigestion with spring exacerbatations,' 'dysentery,' 'pernicious anemia,' 'eczema,' 'sunburn,' 'epileptiform seizures,' 'vaginitis,' and obscure abdominal pains suggesting diseases of the ovaries, appendix or gall bladder." A specific change in the blood of known pellagrous cases might, therefore, serve as a criterion for diagnosis of these obscure conditions mentioned above, and for those cases designated by various authors as "pellagra *sine* pellagra."

About 1 year ago the author noticed that the erythrocytes of pellagrous blood caused more rapid decolorization of iodine solutions than other human erythrocytes, whether normal or pathologic. After a series of experiments designed to test this observation, there was developed a technique which promises to be of value as a clinical laboratory test in the diagnosis of pellagra.

**Reagents.** *Alcohol-ether Mixture.* A mixture of 3 volumes of 95 per cent ethyl alcohol and 4 volumes of ether (commercial or anesthetic ether may be used; chemically pure ether has not been tried).

*Iodine Solution.* Accurately prepared Lugol's solution (5 per cent iodine in 10 per cent potassium iodide).

*Color Standards.* Prepare a 3 per cent potassium dichromate solution and from this make the following dilutions: 1 to 5, 1 to 10, 1 to 20, 1 to 40, 1 to 80, 1 to 120, 1 to 240. Place these standards in a series of test tubes of the same internal diameter.

**Procedure.** *Liquid Petrolatum.* Five cubic centimeters samples of normal or nonpellagrous (control) and of suspected pellagrous venous blood are withdrawn and quickly introduced into 15 cc. centrifuge tubes containing 5 cc. of liquid petrolatum. *The time of collection of each specimen must be recorded.* As each sample is collected, the tube is stoppered and shaken very vigorously until the blood is defibrinated. This may best be accomplished by striking the stoppered end of the tube against the palm of the opposite hand. The specimens are then allowed to stand for 30 to 45 minutes, after which they are again vigorously shaken and centrifuged at 1000 revolutions per minute for 5 minutes. Before the second shaking it is advisable to remove the stoppers momentarily to permit the entrance of air for adequate oxygenation. When the tubes are removed from the centrifuge three distinct layers may be distinguished, namely, an upper layer of fibrin and oil, a middle layer of serum and a lower layer of erythrocytes, leukocytes, etc., which the author shall designate the erythrocytic layer. If any sample has not been properly defibrinated, clots will be present in the lower layer. Such samples should be discarded. One cubic centimeter samples of the erythrocytic layers are now transferred by means of serum pipettes to test tubes of the same diameter as those of the standards. In the removal of these samples from the erythrocytic layer, care must be taken that no oil, fibrin or serum enters the pipette by capillary action as it passes through the two upper layers.

Exactly 1 hour after taking the venous blood specimen, add to the corresponding erythrocytic sample, slowly and without shaking, 5 cc. of the alcohol-ether mixture and stopper the tube tightly. After the alcohol-ether mixture has been added to all samples, let them stand for approxi-

mately 6 hours at room temperature (25° to 30° C.). At the end of this time add in rapid succession to each tube by means of an accurate micro pipette (Folin micro blood pipette or Kahn serologic pipette) a 0.1-cc. portion of the iodine solution. Mix gently and replace the stoppers.

As the mixtures stand there will be noted a gradual diminution of color in each tube, but a greater decolorization in the pellagrous samples. Within 3 hours the extract of pellagrous blood may be completely decolorized while other samples are not. The most constant difference occurs after the tubes have stood about 12 hours. At this time compare the colors of the alcohol-ether extracts with the potassium dichromate standards. The color range of these standards represents that of most samples which have stood 12 hours. Occasionally, however, a pellagrous sample may be completely decolorized, and other samples may be darker than the 1 to 5 standard.

**Interpretation.** On the basis of cases studied, if the color of the unknown matched that of a standard two shades lighter than the nonpellagrous sample, a mild condition of pellagra was apparently indicated. If it compared with a standard three shades lighter than the normal, a moderately developed condition of pellagra was considered to be present. If the unknown compared with or was lighter than the fourth tube from the nonpellagrous or normal, advanced severe pellagra existed. Often in severe cases of pellagra the extract was completely decolorized at the end of or before 12 hours. Reactions have been designated, according to the above method of interpretation, as mild, moderate, severe and negative.

Conclusions relative to the interpretation of the test have been reached by a study of over 150 hospital and dispensary cases, including a variety of diseases, 50 of which were pellagrous. In this series it was found that definitely diagnosed untreated pellagra cases always gave very positive reactions. No other pathologic condition gave positive reactions except certain cases with varied complaints and obscure diagnoses, and other cases with variable complaints in which pellagra was suspected by the attending physician. Only 5 cases of definitely diagnosed pellagra which gave positive reactions were tested after treatment with yeast. In these cases, after an average of 1 month's treatment with yeast the reaction changed from severe to mild, or negative. Mild reactions were given only by treated cases of definitely diagnosed pellagra, and by some suspected cases which were not definitely diagnosed. Moderate reactions occurred in some of the suspected and undiagnosed cases, in some of the untreated pellagrins, and in some treated cases of pellagra. Severe reactions occurred only in definitely diagnosed, untreated cases of pellagra, in 3 of the suspected pellagra cases, and in some undiagnosed cases in which pellagra was not suspected. The following table gives a summary of conditions tested.

In the suspected and in the undiagnosed cases giving positive reactions, it is my belief that pellagra probably existed. It is in

TABLE 1.—RESULTS OF IODIN DECOLORIZATION TEST.

Diagnosis.	Reaction.	Number of cases.
Definitely diagnosed untreated pellagra . . .	Moderate to severe*	37
Definitely diagnosed treated pellagra, treatment of 2 to 4 months' duration . . .	Negative to mild and moderate reactions	10
* Suspected pellagra, not definitely diagnosed	Mild to moderate and severe	6
Active pellagra complicated by other diseases	Severe	3
Undiagnosed cases, pellagra not suspected . . .	Moderate to severe	8
Undiagnosed cases, pellagra not suspected . . .	Negative	4
Addison's disease . . . . .	Negative	1
Carcinoma of the pancreas . . . . .	Negative	1
Epidemic encephalitis . . . . .	Negative	3
Lateral sclerosis . . . . .	Negative	1
Arterial hypertension . . . . .	Negative	3
Tuberculosis of the lungs . . . . .	Negative	5
Syphilis . . . . .	Negative	5
General paresis . . . . .	Negative	14
Tabes dorsalis . . . . .	Negative	1
Dementia precox . . . . .	Negative	20
Manic-depressive . . . . .	Negative	4
Granuloma fungoides . . . . .	Negative	1
Pernicious anemia . . . . .	Negative	3
Diabetes mellitus . . . . .	Negative	3
Myocardial disease . . . . .	Negative	4
Multiple arthritis . . . . .	Negative	4
Cirrhosis of liver . . . . .	Negative	1
Acute bronchitis . . . . .	Negative	2
Carcinoma of rectum . . . . .	Negative	1
Psychoneuroses . . . . .	Negative	4
Hyperthyroidism . . . . .	Negative	2
Psoriasis . . . . .	Negative	3
Carcinoma of cervix . . . . .	Negative	1
Carcinoma of stomach . . . . .	Negative	2
Myelogenous leukemia . . . . .	Negative	1
Chronic nephritis . . . . .	Negative	3
Ulcerative colitis . . . . .	Negative	1
Normal . . . . .	Negative	6
Total . . . . .		168

\* Reaction after treatment: Five cases observed and all became mild or negative after treatment.

these cases that the test would be especially valuable, and it remains for experience with the test to determine the reliability of the procedure as a criterion of diagnosis.†

† We feel that this preliminary note should be supported by the following statement which did not come to us through the author. Dr. M. R. Everett, Professor of Biochemistry and Pharmacology at the University of Oklahoma, has replied to our letter as follows: "A theoretical consideration of the possible pathology of glutathione metabolism in pellagrins led him to investigate the effects of iodine on the blood of hospital patients. . . . During this work I was almost a constant observer of his technique and to me the results were very striking, pellagrous samples of blood being easily distinguished from all the others, as described in his paper. Often series of samples were numbered and kept as unknowns until the laboratory tests were completed. . . . Dr. Campbell had some of his associates do the technical work of the test to provide a further check. In fact, I am certain that the only possible error in his test would have to be some insidious factor, such as an unknown impurity in his reagents (and, of course, we used various samples of reagents) but, of course, this could only be found by others trying the test. . . . Also Dr. Campbell has had the clinical advice and aid of some of our best clinical associates here. . . ."



**Discussion.** A detailed discussion of the possible chemical basis of this test must be postponed. Apparently the essential factor is a catalyst, since it is merely the rate of disappearance of the iodine which serves for differentiation. After a sufficient length of time both pellagrous and nonpellagrous extracts are totally decolorized. The very gradual reduction of the iodine in the above procedure points to something other than glutathione as the pertinent reducing factor. This has been substantiated by glutathione determinations in a number of these pellagrous bloods by the method of Woodward and Fry.<sup>2</sup> The glutathione content of these samples was found to be practically the same as that of the normals.

Delaville and Kowarski<sup>3</sup> state that there are two fractions in blood concerned in the reduction of iodine, namely, a rapid one which they believe to be glutathione and a slow fraction, extremely complex, which reduces iodine at a very variable rate. My experiments have shown that the factor responsible for the gradual decolorization of iodine in the alcoholic-ether-erythrocytic mixture was constantly more active in pellagrous samples. Attempts have been made to simplify the procedure of the test described by using oxalated blood, laked corpuscles and whole blood. The results were unsatisfactory and the more complicated procedure described above is the only successful one thus far devised. Further study is in progress.

**Conclusions.** Pellagrous blood reduces iodine solutions at a constantly greater rate than that of any other blood thus far examined. This phenomenon is made the basis of a test which promises to be of clinical value in the diagnosis of pellagra. Many pathologic conditions have not been examined, and it is possible that further work will disclose that other conditions simulating pellagra may give positive reactions. However, the phenomenon of increased rate of iodine decolorization by the erythrocytes in pellagrous blood may lead to fruitful information bearing on the etiology of pellagra, certain entities of avitaminosis and malnutrition.

**NOTE.**—Appreciation is extended to administrative and faculty members of the University of Oklahoma School of Medicine and to the Superintendent of the Western Oklahoma State Hospital for the privileges of studying clinical material and for the use of laboratory facilities; also to Dr. M. R. Everett for helpful suggestions.

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## MAINTENANCE OF NORMAL BLOOD IN PERNICIOUS ANEMIA BY MEANS OF INTRAMUSCULAR INJECTIONS OF A SOLUTION OF LIVER EXTRACT.\*

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In a patient with pernicious anemia the maintenance of an essentially normal condition of the blood and a satisfactory state of health with sufficient liver substance to prevent a relapse is quite as important as that of treating the patient whose blood is in a state of relapse.

This paper deals particularly with the problem of the maintenance care of those patients treated with intramuscular injections of the Solution Liver Extract (Lederle), described in a previous paper.<sup>1</sup> One hundred and one patients have been treated in this manner during a period of 16 months. Six received the extract intravenously at some time during the period of observation. A few of the patients have taken liver or liver extract (fraction G of Cohn) by mouth in place of the injections for varying periods of time, and rarely small amounts of liver substance have been ingested in addition to that received by injection.

Of the 101 patients under discussion 44 received their first parenteral treatment during the time that they were patients in the hospital, and in the majority the blood was in a state of relapse. Fifteen patients who first came under observation with red blood cell counts under 4,000,000 per c.mm. were treated as ambulatory patients. The remaining 42 patients were changed to this form of treatment, having previously been under observation on a regimen of liver or liver extract by mouth. The change in form of therapy was frequently made at the patient's request, or particularly in those patients whose initial blood level was below normal, either because oral treatment was neglected or because a normal blood level was not maintained readily by means of the ingested liver substance. The entire group of patients reported represents a consecutive series and includes many definitely resistant cases.

**Method of Treatment.** The usual and advised procedure has been to give an initial subcutaneous injection of 0.2 cc. of solution followed in 1 hour by a similar injection of 0.4 cc. If by the end of 1 or 2 hours no evidence of sensitivity (indicated by a chill and rise in temperature) has appeared, a deep intramuscular injection, consisting of 6 cc. of solution

\* This study was aided by a grant from the De Lamar Mobile Fund of the Harvard Medical School.

prepared from 200 gm. of liver, is given. At any time during the next 12 hours a second similar injection is given. At an interval of from 1 to 4 weeks after the initial therapy just described injections are resumed in 3-cc. doses\* (prepared from 100 gm. of liver) at weekly intervals until the blood has reached a normal level (5,000,000 or more red blood cells), and then at intervals as indicated by the requirements of the individual patient. An effort has been made to extend the interval between injections only when the level of the blood count and the patient's condition warranted such a change. The presence of symptoms associated with spinal cord damage has been used as an indication for intensive treatment, even though the blood level was high. With such a policy in mind, and counting the number of red blood cells at the time of each intramuscular injection, it has been possible to extend the interval between injections to as long as 6 weeks and still maintain the patient and his blood in a satisfactory condition.

The intramuscular injections are given usually into the gluteal muscles, care being taken to avoid the region of the large bloodvessels and nerves. A 1.5-inch, 21-gauge needle is inserted by means of a quick thrust which renders the procedure essentially painless. The syringe containing the solution of liver extract is fitted to the needle, the plunger withdrawn slightly to be sure that blood cannot be withdrawn, and then the solution is injected slowly. In the event that blood appears in the needle it is to be withdrawn and reinserted.

Iron, usually in the form of capsules of ferrie ammonium citrate,† has been given in doses of 3 gm. daily for varying lengths of time at some period during the course of treatment of the majority of the patients. With the rapid production of red blood cells, which occurs during the course of this form of treatment, the available iron reserve is depleted with a resulting apparent "secondary" anemia. This striking relative insufficiency of hemoglobin has occurred rarely in those patients ingesting whole liver, probably because of the iron contained therein, and because of slower regeneration. Generally the use of 100 to 200 gm. of ferric ammonium citrate given in the dose mentioned above is sufficient to bring the hemoglobin content of the cells to normal, and rarely is a second course of treatment necessary. Notable improvement in the patient's general condition, and particularly in the symptoms generally considered to accompany nerve damage, has occurred coincidently with the use of iron.

**Treatment During Relapse.** Although a discussion of the results of treatment by means of the intramuscular injection of the solution of liver extract during relapse was presented in a previous paper,<sup>1</sup> the results obtained in a much larger group are now available. Satisfactory improvement in the condition of the patient and of the blood has occurred in each instance. There has been, however, considerable variation in the amount of solution used and the time interval necessary in order to bring the red blood cell count and hemoglobin to normal levels. These variations are to be expected and depend upon various circumstances relative to the patient's condition.

\*The dose advised refers only to Solution Liver Extract (Lederle) which was used in each instance. Inadequate dosage must be avoided if less concentrated extracts are used.

† Capsules of Ferric Ammonium Citrate (Lederle), 0.5 gm. each.

The 44 patients first treated in the hospital had initial red blood cell counts varying between 1,000,000 and 4,500,000; 10 have either been discharged to other physicians or have been followed for only short periods of time; 34 have been followed for a period of time sufficient for the red blood cells to reach a level of 4,500,000 or more. In order to accomplish this the number of injections of extract derived from 100 gm. of liver (usually 3 cc.\*) given generally varied from 5 to 10 and over periods of time varying from 20 to 50 days. The extremes varied from 2 injections in 10 days to 24 in 177 days. The longer periods of time and larger amounts of material were needed in those patients having complicating conditions.

Those treated as ambulatory patients have remained actively at work, some at hard manual labor, throughout their course of treatment. All 15 of this group whose initial red blood cell counts varied between 2,100,000 and 4,000,000 have also been followed until the red blood cell level was 4,500,000 or more. Ten reached this level in from 7 to 50 days and all but 2 in less than 60 days. The amount of liver extract used varied from 1 injection of 3 cc. (derived from 100 gm. of liver) to 8 such injections, except that 1 patient received 13 such injections in a period of 89 days.

In view of the fact that rest is generally considered to be important for the most satisfactory improvement of the blood, it is interesting to note the rapid improvement and the small amount of liver solution used intramuscularly in the ambulatory group. Because the results of treatment have been so little, if at all, retarded by activity it would seem advisable to allow a greater amount of activity for the patients treated in relapse in the hospital, especially the older ones in whom pulmonary complications and phlebitis must be guarded against.

**Maintenance Treatment.** The aim has been to establish for each patient the optimal treatment necessary for his or her needs and also to be as economical as possible in the amount of material used. It is vastly more important to the patient to be kept in good health than it is to attempt to economize by the use of minimal or sub-optimal doses. As with the use of liver substance by mouth, the proper dosage must be determined by the condition of the patient and by the trend of the red blood cell count as recorded at intervals over a period of time. The red blood cell level should remain preferably at or above 5,000,000 cells per c.mm., and the cells themselves should be normal in size and shape. Although the occurrence of symptoms of illness is an important indication of inadequate treatment, the absence of symptoms or a feeling of well-being is neither sufficient evidence that the blood is remaining

\* In all but a few of the earlier injections this has been 3 cc. of solution. The earlier solution used and described previously was less concentrated.

normal nor that the patient is in satisfactory condition to avoid progression of the nerve disturbances.

The group of patients under observation has been maintained in a generally better state of health than a similar group observed under oral treatment. This fact is probably to be explained by the relative ease of administering optimal amounts of effective material in a manner favoring better absorption and utilization of the active substance and by the avoidance of gastrointestinal symptoms frequently observed in patients under treatment with liver by mouth, rather than on the basis of some unusual effect of the solution of liver extract. As was noted in a previous paper,<sup>1</sup> improvement in the symptoms occurring with peripheral nerve damage or spinal cord sclerosis has been unusually striking. This effect is no doubt also the result of the rapid and marked improvement possible through the ease of administration of adequate amounts of liver substance by the intramuscular route.

Eighty-one patients have been observed over a sufficiently long period of time to give one a clear idea of their maintenance requirements. This group is made up of 27 of the 44 patients first treated while in the hospital, 12 of those treated as ambulatory patients whose initial red blood cell counts were below 4,000,000, and 42 patients in whom the intramuscular treatment was introduced in place of some other. The red blood cell count when intramuscular treatment was started in the last mentioned group of 42 patients varied between 3,800,000 and 6,800,000. In 20 instances the count was below 4,500,000, and in 13 it was 5,000,000 or more.

In a few instances the lower blood levels in this group were due to failure on the part of the patient to follow out the prescribed treatment either because of an inability to obtain liver or a potent substitute for it, or a temporary inability to ingest it. The majority of those whose recorded initial blood level was below normal were taking average or even unusually large amounts of liver substance by mouth, with failure to maintain a satisfactory physical or blood condition. The difficulty to maintain readily a satisfactory condition with reasonable amounts of material has been due to the presence of chronic infections, arthritis, marked spinal cord sclerosis, unusual worry or perhaps old age. In the remainder of the patients of this group the change to intramuscular treatment has been made in order to influence favorably the difficulties occurring with spinal cord sclerosis, at the request of the patient, usually because of difficulty with the ingestion of the prescribed amount of liver, or through a desire to lessen the expense of treatment.

Typical examples of the manner in which treatment has been carried out in the patients under discussion are shown in Table 1. The red blood cell counts and hemoglobin levels recorded represent only the last determination made before a change to another treatment interval.

The number of patients receiving an injection of 3 cc. (derived from 100 gm. of liver) of the solution of liver extract at the various time intervals is shown in Table 2, together with the extremes and averages of the red blood cell levels in the patients treated at the several intervals.

TABLE 1.—THE MAINTENANCE TREATMENT WITH INTRAMUSCULAR INJECTIONS OF SOLUTION OF LIVER EXTRACT AS CARRIED OUT IN 81 PATIENTS WITH PERNICIOUS ANEMIA.<sup>1</sup>

Case No.	Initial.		7 days.				14 days.				21 days.				28 days.				35 days.			
			No. 7-day intervals.	Resulting.		No. 14-day intervals.	Resulting.		No. 21-day intervals.	Resulting.		No. 28-day intervals.	Resulting.		No. 35-day intervals.	Resulting.						
				R.B.C.	HB.		R.B.C.	HB.		R.B.C.	HB.		R.B.C.	HB.		R.B.C.	HB.	R.B.C.	HB.			
	R.B.C.	HB.	R.B.C.	HB.	R.B.C.	HB.	R.B.C.	HB.	R.B.C.	HB.	R.B.C.	HB.	R.B.C.	HB.	R.B.C.	HB.						
64	4.6	14.5	3	5.2	16.3																	
67	4.2	12.8	7	5.6	15.2	3	5.4	14.5														
78	4.3	12.1	3	5.0	13.5	4	5.1	13.9	4	6.1	15.9											
85	4.5	11.7	4	5.2	14.3	5	5.1	14.1				3	5.3	16.3								
92	4.1	13.5	4	4.9	12.8	2	5.2	13.9	2	5.1	14.4				2	5.3 14.1						

R.B.C. = red blood cells in millions per cubic millimeter.

HB. = hemoglobin in grams per 100 cc. of blood.

<sup>1</sup> Injections of 3 cc. extract prepared from 100 gm. liver given at the recorded interval.

TABLE 2.—THE INTERVALS BETWEEN TREATMENTS AND THE RED BLOOD CELL COUNTS MAINTAINED WITH INTRAMUSCULAR INJECTIONS OF SOLUTION OF LIVER EXTRACT IN 79 PATIENTS WITH PERNICIOUS ANEMIA.

Interval between injections, weeks.	Number of patients.	Range of final red blood cell counts.*	Average red blood cell counts.†
6 . . . . .	3	4.8-5.7	5.2
5 . . . . .	8	4.6-6.4	5.5
4 . . . . .	11	5.1-6.4	5.6
3 . . . . .	22	4.7-6.1	5.5
2 . . . . .	24	4.5-6.2	5.1
1 . . . . .	11	4.6-5.5	5.2

\* In millions per c.mm.

One other patient with an initial red blood cell count of 2,380,000 received injections of solution totaling that obtained from 1000 gm. of liver in a period of 39 days. She has received no further treatment with liver substance during a period of 500 days, during which time her red blood cell count has varied from 5,100,000 to 8,400,000, and the hemoglobin has averaged 16.4 gm. per 100 cc. of blood. Another patient, whose initial red blood cell count was 3,480,000, received 11 injections representing the solution derived from 1100 gm. of liver in 62 days. No further liver treatment has

been received by the patient during a period of 308 days, during which time the red blood cell count has varied between 4,800,000 and 6,100,000 cells and the hemoglobin level has averaged 15 gm. per 100 cc. of blood.

The patients still under treatment at 7- or 14-day intervals have been under treatment generally for shorter periods of time than those receiving treatment at less frequent intervals.

Treatment has been very conservative, and the red blood cell levels have been maintained almost constantly above 5,000,000. In many instances it would no doubt be possible greatly to increase the interval between injections, but for one reason or another this has not been as yet deemed advisable. Because of extraordinarily high red blood cell levels in 2 patients, it has been possible to discontinue treatment for long periods of time. This may prove to be possible in other cases under this form of treatment, but, of course, should only be done when red blood cell counts can be made at frequent intervals.

Storage in the body of the substance active in stimulating formation of the red blood cells is suggested by the result obtained in these 2 patients. Richter, Ivy and Kim<sup>4</sup> have presented evidence which suggests that the liver may have the ability to store the "active principle" of liver, which is in line with the opinion previously expressed by the author<sup>5</sup> that "disturbances in the biliary system or liver may be of even more immediate etiologic importance (in pernicious anemia) than are the gastric changes." Another feature of the treatment has been the frequent occurrence of a steadily increasing red blood cell count as the interval between injections was increased. This suggests that any excess of the active substance over that which is actually used for the immediate production of blood is stored for future utilization.

**Reactions.** Reactions or complications following the intramuscular injection of the solution of liver extract have been negligible and of little practical importance in this series of cases treated with nearly 1000 injections. Two patients reacted after the first injection, one a small intracutaneous dose, in such a manner that sensitization to liver was suspected. After a series of small doses in increasing amounts both have continued the injections uneventfully. One patient developed urticaria with nausea following the 12th injection given on a very hot day. Very slight urticaria occurred following the next 2 injections, but has not occurred since. This patient first presented herself for intramuscular treatment with generalized urticaria, which had appeared following the ingestion of 2 vials of liver extract (Colm fraction G). Hare,<sup>2</sup> Strandell and Hammar<sup>3</sup> and others have reported urticarial rashes following the intramuscular injection of various liver extracts. On a few occasions the patient has felt faint after the injection. This has occurred in unusually

nervous persons who have received many other injections without such an occurrence. Hematoma has occurred at the site of injection twice. Infection has not occurred.

**Results and Conclusions.** Intramuscular injections of the solution of liver extract, given to patients in relapse or whose condition was unsatisfactory because of complications, instigated a remission in each instance, as is to be expected with treatment by means of the ingestion of liver or an actively potent substitute. The beneficial effects of intramuscular injections occurred sooner and more strikingly than with peroral treatment.

Maintenance treatment carried out by the same means in 81 instances for sufficiently long periods of time to allow analysis of the amount of solution needed, shows that an intramuscular injection of the amount of solution derived from 100 gm. of liver (generally 3 cc.), at intervals varying from 1 to 6 weeks, has maintained all of these patients in a satisfactory state of health with a normal condition of the blood. Improvement in the symptoms generally considered to accompany spinal or peripheral nerve damage has occurred regularly and often strikingly, and progression of these disturbances has not occurred in any patient after the blood condition has become essentially normal. Relapse has not occurred in any patient continuing under observation and treatment.

The anemia diet, but not including liver, as previously suggested for the patient with pernicious anemia, has been advised in each instance, and a course of large daily doses of iron (ferrie ammonium citrate) has generally been prescribed at some time during the course of treatment, in order to allow the hemoglobin level to keep equal with the course of the rapid red blood cell formation. This has been of distinct benefit in improving the physical condition of the patient.

It has been possible with the use of the intramuscular treatment to maintain this group of patients in a better state of health and with a more satisfactory condition of the blood than was possible by means of treatment by mouth; the prolonged treatment has been more economical to the patient; and this method of administration of liver substance has usually been better liked.

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## A STUDY OF A LYMPHOCYTIC HEMOGRAM.

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ARNETH,<sup>1</sup> in his monumental work on the polymorphonuclear leukocyte, laid the basis for subsequent studies on the nuclear changes in the granulocyte, culminating in the useful and well-known Schilling index. He also published an index of nuclear variation in the lymphocyte, to which he attached maturative significance. These studies, however, have not been verified.

In a recent article Wiseman<sup>2</sup> has reviewed the criteria of the age of lymphocytes and has classified them as follows:

1. Basophilia of the cytoplasm. The association of basophilia of the cytoplasm with the youth of other blood cells is well known. The so-called reticulocyte is an example of this characteristic in the immature erythrocyte. Basophilia is also well illustrated in the myeloblast and megakaryoblast.

2. Mitochondria. Cowdry<sup>3</sup> states that as the cell matures, the number of mitochondria diminishes.

3. Size of the cell. This is a subject of considerable controversy, and some authors<sup>4,5</sup> have regarded the large lymphocytes as the younger, while others<sup>6,7,8,9</sup> have considered the small lymphocytes the more youthful. Most investigators studying fixed stained preparations call the large cells older, while those who use supravital technique hold the reverse.

4. Miscellaneous features, such as motility, vacuoles, chromatin content of the nucleus, proportion of nucleus to cytoplasm, shape of nucleus and azure granules.

Wiseman<sup>2</sup> studied normal bloods and those in which he would expect a physiologic or pathologic hyperplasia of lymphoid tissue, such as new-born rabbits and rabbits with active tuberculosis. The degree of basophilia in fixed preparations and the number of mitochondria by the supravital method in the same drop of blood were found to agree. He also found that the shape of the nucleus bears no relation to the degree of basophilia or the number of mitochondria. The chromatin content of the nucleus was not greatest in those cells which were least basophilic. Nucleoli, however, were visible only in the nuclei of cells with deeply basophilic cytoplasm and fine chromatin. No cytoplasmic structure in the living lymphocyte could be identified with the azure granules of the fixed cell, and this suggests that these granules are a precipitation brought about by fixation, possibly evidencing some functional

TABLE 1.—NORMALS.

Case.	Sex.	Age.	Diagnosis.	Date.	W. B. C.	Neut. polys., per cent.			Lymph., total per cent.	Lymph., per cent.		Mon., per cent.	Eos., per cent.	Bas., per cent.	Clinical data.
						Young.	Band.	Mature.		Yg.	Med.				
1	M	20-40 1-12 1-12 mos. 32	Average of normal adults Average of normal children Average of normal infants Normal	..	7,000	..	..	4	63	5	50	45	1	0	25 cases.
				..	8,000	..	..	2	41	10	60	30	1	1	25 cases.
				10/6	10,000	..	..	2	28	10	65	25	2	1	25 cases.
				10/8	7,000	..	..	1	69	17	45	38	6	1	Well.
				10/8	7,000	..	..	3	75	14	72	14	6	..	Head cold; temp. 100°.
2	F	30	Normal	10/12	4,800	..	..	..	64	15	59	26	2	..	Well.
				10/14	5,200	..	..	3	54	6	55	39	4	1	Well.
				10/14	6,800	..	..	1	57	8	54	38	6	..	Well.
				11/4	7,000	..	..	..	63	8	54	38	1	..	Well.
				10/15	8,000	..	..	1	61	3	41	56	7	..	Well.
				10/28	11,200	..	..	2	71	5	45	50	6	..	Well.
				11/4	8,100	..	..	1	58	9	66	25	..	..	Cold.
				11/9	9,600	..	..	..	60	11	58	31	4	..	Pains in abdomen for
				11/11	5,100	..	..	..	48	10	60	30	3	..	1 week; up and
				11/15	11,000	..	..	1	60	5	64	31	1	..	about.
				11/18	5,100	..	..	..	48	11	52	37	4	2	Well.

TABLE 2.—LEUKEMIC CASES.

Case	Sex	Age	Diagnosis	Date	W. B. C.	Neut. polys., per cent.			Lymph., total per cent.	Lymph., per cent.	Mon., per cent.	Myelo- cytes, per cent.	Pre- myelo- cytes, per cent.	Myelo- blasts, per cent.	Clinical data.
						Young.	Band.	Mature.							
1	M	58	Lymphatic leukemia	10/15	200,000	..	2	13	85	95	5	0	..	..	..
2	M	10	"	8/2	31,000	..	..	8	92	60	35	5	..	..	..
3	M	55	"	9/3	42,800	..	..	25	73	39	51	10	2	2	..
4	M	19	"	10/18	5,000	..	..	19	77	78	22	0	..	..	..
5	M	60	"	7/20	140,000	..	..	7	92	0	100	0	1	..	..
6	M	62	"	10/5	120,000	..	..	1	99	0	100	0	..	..	..
7	M	59	Myeloid leukemia	10/22	170,000	..	2	2	96	0	97	3	..	..	..
				10/28	150,000	..	..	2	98	0	95	5	..	..	..
				11/5	150,000	..	..	2	97	0	96	4	1	..	..
8	F	60	"	8/20	160,000	..	..	2	97	20	80	0	..	10	..
				8/31	6,000	..	..	..	(on exam. many fields)	..	..	..	..	..	..
				9/12	30,000	..	18	8	25	30	61	6	..	2	..
				9/20	300,000	15	24	..	14	35	65	0	..	5	..
9	M	36	"	9/20	300,000	..	..	..	..	8	50	12	..	17	..
10	M	45	"	9/20	300,000	..	..	..	(on exam. many fields)	..	..	..	..	..	..



10	M	36	Multiple neuritis; etiology unknown	9/22	17,000	28	11	11	0	70	30	3	51	Temp. 101°; biopsies for trichiniasis negative.
				9/25	16,000	32	8	9	0	75	25	3	56	Temp. 100°.
				9/29	12,800	37	8	9	0	78	22	3	53	
				10/3	16,600	44	12	31	41	50	9	3	40	
				10/6	15,600	39	13	37	6	58	62	0	44	
				10/10	16,400	37	6	0	84	16	16	5	52	
				10/20	13,400	25	12	33	50	17	33	50	59	
				10/27	12,200	33	15	54	46	0	92	2	25	
				11/3	20,000	33	10	60	92	18	0	1	54	Unimproved.
11	F	52	Carbuncle of upper lip	10/29	32,200	71	6	16	68	16	0	1	54	Temp. 104°.
				11/2	28,700	60	4	25	75	0	0	2	..	Progressively worse.
				11/5	53,600	32	8	37	63	0	0	2	..	
				11/9	30,800	87	5	51	49	0	0	2	..	Died.
				11/12	32,600	82	6	58	33	9	0	2	..	In hospital since 8/2, running glandic temp.; biopsy of gland showed enormous proliferation of endothelial cells; temp. now between 99 and 100°, feels well.
12	M	43	Inguinal adenitis	10/23	14,800	19	50	4	48	48	4	4	..	Temp. 101°.
				10/26	9,500	59	29	3	53	44	7	4	..	History and Vidal suggestive of typhoid; developed signs in chest.
				11/5	7,800	48	40	3	66	27	7	2	..	Improved.
13	M	39	Typhoid?; broncho-pneumonia	10/22	7,000	55	41	9	40	51	2	2	..	
				10/26	9,400	68	23	22	56	22	2	2	..	
				10/29	6,800	71	17	12	60	38	5	5	..	
				11/2	7,400	61	34	36	35	29	5	10	..	
				11/5	8,600	48	38	5	45	50	10	10	..	
				11/9	5,600	75	15	20	33	47	3	3	..	Improved.
				11/12	4,000	38	32	18	42	40	3	3	..	Temp. 102°.
14	F	44	Pneumonia; aneurysm of aorta or possible mediastinal neoplasm	11/16	5,400	58	36	3	27	70	1	1	..	Gradual improvement; temp. 100°.
				10/22	26,200	76	8	12	62	26	9	7	..	Slight relapse; temp. 103°.
				10/26	19,000	72	17	15	56	29	7	10	..	Improvement; temp. 100°.
				10/29	16,400	60	27	18	51	31	10	10	..	Temp. 100.5°.
				11/2	13,200	68	19	31	47	22	9	9	..	Temp. 101°; slight operation.
				11/5	8,400	43	41	29	42	20	11	3	..	Temp. 99°.
				11/9	18,800	88	9	22	56	22	3	3	..	Type I pneumococcus; temp. 103°.
15	F	10	Chronic osteomyelitis of right femur	11/12	6,600	42	47	12	34	51	10	10	..	Improved.
				10/21	16,400	53	37	8	67	25	3	3	..	Up.
				10/25	21,000	63	29	3	70	27	3	3	..	Temp. 101.5°.
				10/28	23,800	63	26	3	57	40	5	5	..	Temp. 100°; menstruating.
				11/1	13,400	59	27	27	59	14	6	2	..	Improved; temp. 99°.
				11/4	15,000	52	42	26	33	41	2	3	..	Well.
				11/10	9,800	37	56	10	44	46	2	2	..	
				11/17	15,400	47	42	7	38	65	2	2	..	
16	M	48	Lobar pneumonia	11/1	7,000	81	6	16	68	16	6	6	..	
				11/4	7,600	67	29	10	63	27	3	3	..	
				11/7	7,200	50	40	35	45	20	6	6	..	
				11/10	4,400	45	45	13	70	17	5	5	..	
				11/14	6,400	62	36	11	41	45	3	3	..	
				11/1	10,000	60	30	24	73	3	9	9	..	
				11/1	15,200	58	30	16	61	23	0	3	..	
17	F	21	Grippe	11/9	10,300	44	49	12	67	21	5	5	..	
				11/11	11,660	48	47	49	36	15	4	4	..	
				11/13	14,200	62	29	20	41	39	6	6	..	
				11/20	8,000	61	26	7	50	43	7	7	..	

activity of the mature cell. It, therefore, seems that basophilia of the cytoplasm is a constant and reliable criterion of the age of lymphocytes.

With these facts in mind studies were undertaken on a series of normal and diseased adults and children to see if a classification of lymphocytes according to the degree of basophilia would be of clinical value.

The cases selected were widely diversified and represented all types, from the very sick to ambulatory patients with minor complaints. In establishing the normals, single observations were used in the majority of instances. The sick patients were studied at bi-weekly intervals during their stay in the hospital, and a small series of normals were followed at similar intervals over a time interval corresponding to the average stay of a patient in the hospital.

This report embodies 75 normals, equally divided among adults, infants and children, 10 normals followed at bi-weekly intervals for 1 month and 150 patients followed at bi-weekly intervals during their stay in the hospital.

**Technique.** White and differential counts were done for each observation. The total white counts were done with carefully standardized pipettes, and the films were made on slides, care being taken to keep them "rim free." The stain used was Wiseman's Wright-Giemsa. An average of 200 leukocytes was counted and the lymphocytes were divided into three classes: Y (young), M (medium) and O (old) forms, according to the degree of basophilia of their cytoplasm. The Y forms have a deep blue cytoplasm, the M forms moderately blue and the O forms are faintly blue or colorless, and usually show azure granules in the cytoplasm, although the M forms occasionally show them too. A little practice with the above technique will make the three divisions clear. It is necessary, however, that the lymphocytes be examined in those parts of the film in which the red cells do not overlie, as in the thick portions of the film the lymphocytes are likely to overstain. The total number of lymphocytes is noted as well as the number of Y, M and O forms, and the percentages of each are then easily calculated, the procedure being similar to that followed in enumerating the different forms of polymorphonuclears when doing the Schilling index. When the total number of lymphocytes is low it is best to count 300 to 500 white cells to insure more accurate results. The polymorphonuclear leukocytes were tabulated according to the Schilling method in each instance in order to compare the granulocytic and lymphocytic indices.

The observations are to be found in the Tables, pages 279 to 281.

**Discussion.** Analysis of the experimental data shows that there is a fairly constant lymphocytic formula for normals. For adults this can be expressed as Y forms, 5 per cent; M forms, 50 per cent; O forms, 45 per cent. Variations occur in this formula under different conditions, and we can, therefore, speak of a shift to the left or to the right of the lymphocytic index, depending upon whether the number of younger forms is greater or less than normal. A comparison with the Schilling index in each case shows that the two do not run parallel. The lymphocytic index is not as stable as the Schilling and will shift to the left just as easily in a mild

as in an acute infection. Even though the lymphocyte formula cannot be used to gauge the severity of an infection, its shift to the left in these conditions nevertheless indicates that lymphocytes take an active part in combatting bacterial invasion. This is seen by the increase in Y and M forms and the decrease in O forms in practically all cases of infection.

The lability of the lymphocyte hemogram makes it valuable in the detection of minor infections which do not disturb the more stable Schilling index. Interesting and confirmatory evidence for using basophilia as a criterion of the age of lymphocytes is seen in the study of the lymphatic leukemias. The marked increase in the proportion of Y and M forms in these cases represents the well-known hyperactivity of the lymphatic system in these diseases. In the myeloid leukemias there is also an increase in lymphocyte activity and a shift of the index to the left.

It is also of interest to note that, according to the lymphocyte index, most patients are not entirely well on being discharged from the hospital and that the period of convalescence is probably much longer than usually expected. A patient should not be regarded as entirely recovered from an infection until the lymphocyte formula has returned to normal.

**Conclusions.** 1. A lymphocyte hemogram has been studied, using basophilia of the cytoplasm as a criterion of the age of the lymphocytes.

2. The lymphocyte formula is stable in health, but is more labile than the Schilling index, and cannot be used to gauge the severity of an infection. Its shift to the left in infections nevertheless indicates that the lymphocytes take an active part in combatting these conditions.

3. The lability of the lymphocyte index makes it valuable in detecting minor infections which do not disturb the more stable Schilling index.

4. The lymphocyte index is superior to the Schilling in guarding the progress of convalescence, and a patient should not be regarded as entirely well until the lymphocyte formula has returned approximately to normal.

Grateful acknowledgment is due Dr. J. S. Leopold for permission to study cases from the A. Jacobi Children's Division, Lenox Hill Hospital.

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# REVIEWS.

A STANDARD CLASSIFIED NOMENCLATURE OF DISEASE. Compiled by The National Conference on Nomenclature of Disease. Edited by H. B. LOGIE, M.D., C.M., Executive Secretary. Pp. 701. New York: The Commonwealth Fund, 1933. Price, \$3.50.

THE names of the organizations and their distinguished representatives that have aided in or approved of this compilation are as good a guarantee of its value as such evidence can be. In passing one cannot help being curious why pathology was not included in the conference members or coöperating committees. Surely here is a field in which the pathologist has the last and most decisive say!

While one can naturally find many single items for objection, the general scheme is excellent. Using the decimal system throughout, a topographical classification (to 3 or more decimals) begins on page 14, giving 11 main systems (0, body as a whole; 1, integumentary; 2, musculo-skeletal, etc.). On page 50 begins the etiological classification, again with 11 subdivisions (0, prenatal; 1, lower parasites, etc., through x, "unknown or uncertain, the functional reaction to which alone is manifest"). Thus from the classified nomenclature proper (beginning on page 83) we learn for example that *talipes equinus* is listed as 249-0225, i. e., a disease of a joint (24) ninth to be listed, which is an abnormality of structure (02) due to distortion (022), the fifth to be listed (0225). The full index and especially "How to Use the Nomenclature" (page 11) should first be consulted.

E. K.

ENDOCRINE MEDICINE. In four volumes. By WILLIAM ENGELBACH, M.D., F.A.C.P., B.S., M.S., D.Sc., Member of Starr, St. Louis, City, Jewish, Baptist Sanitarium and Maternity Hospitals. With a Foreword by LEWELLYS F. BARKER, Professor Emeritus of Medicine, The Johns Hopkins University School of Medicine, Baltimore. Vol. I. General Considerations. Pp. 460; 139 illustrations and 62 tables. Vol. II. The Infantile and Juvenile Endocrinopathies. Pp. 473; 109 illustrations and 25 tables. Vol. III. The Adolescent and Adult Endocrinopathies. Pp. 862; 255 illustrations and 26 tables. Vol. IV. Bibliography, Index of Names and Subjects. Pp. 117. Springfield, Ill.: Charles C Thomas, 1932. Price, \$35.00 a set.

THIS is an elaborate treatise on endocrinology, with special emphasis placed on thyroid and pituitary, the author having reserved for the future a discussion (which his unfortunate death now prevents) of the islands of Langerhans and of Addison's disease.

Everyone must agree with the author's opening statement that "The recent advances made in the studies of the physiology and pathology of the endocrine glands are considered sufficient justification for compilation of a treatise endeavoring to bring this subject up to date." One would hope, too, that a four-volume work could give a satisfactory summary of the present knowledge of the various phases of this complex subject, even though doubting any one individual's ability to present all the different aspects satisfactorily. We must admire the author's courage, therefore, in undertaking the job single-handed, if not unaided, even though we may recognize that not a few questionable personal interpretations shake one's confidence in the value of the whole production.

Much of the literature is reviewed in a manner that is both careful and up to date, but the discussion is chiefly based upon the author's records of over 2000 patients with endocrine disorders. Thus the Fundamentals—whose advances constituted the “sufficient justification”—occupy but 200 of the 1800 pages of text. Furthermore the method of approach renders consultation arduous, even though the extensive index facilitates search for a given item. The segregation of the individual gland disturbances—often into different volumes—into disorders arising in Infants, Juveniles, Adolescents and Adults, makes a connected survey from the anatomical standpoint difficult and necessitates considerable repetition.

The work is profusely illustrated with photographs of patients, Roentgen rays, charts and detailed case histories. It is of interest in expressing the experience, convictions and classifications of the clinician author, and with its many references to the literature should be valuable to workers in this field.

E. K.

A MANUAL OF EMBRYOLOGY. By J. ERNEST FRAZER, F.R.C.S. ENG., Professor of Anatomy in the University of London; Lecturer at the Medical School of St. Mary's Hospital, etc. Pp. 486; 282 illustrations. New York: William Wood & Co., 1932. Price, \$8.00.

EVEN when existing textbooks on a subject are being kept reasonably up to date, a good new work is almost bound to bring a fresher point of view and give more adequate treatment to recent developments. In this case, the distinguished author is especially qualified to present the advances of the last quarter century in explaining the processes of development of human organs and tissues. The regional method of approach has been followed, as giving a better “connected mental picture of the developing embryo.” Nevertheless a good index—and we commend the black face figures to indicate the chief treatment of a topic—permits one to use the book up to a certain point as a work of reference. All references, however, are omitted, statements made on the authority of others merely being indicated by the author's name in a bracket. Even for the medical student for whom the book is intended this constitutes a grave handicap for broad-minded study. However, even with this restriction, the book will prove useful in medical schools.

E. K.

MEN AGAINST DEATH. By PAUL DEKRUIF. Pp. 363; illustrated. New York: Harcourt, Brace & Co., 1932. Price, \$3.50.

LIKE the Microbe Hunters, Men against Death makes mighty good reading (so contagious is the author's style that an expletive unwittingly slipped in here, only to be replaced by the weaker adjective on re-reading!). We hope that a multitude of medical students and laymen will form the same opinion, so that they may become personally acquainted with more of the outstanding figures of our medical history. After this expression of our feelings, we hope that some objective criticisms will not be misunderstood.

A book which “pretends only to tell the plain story of scientific adventure for plain people” naturally must be evaluated by different criteria than a work of biography or history. We can pass over, then, more easily the colorful hyperbole and gratuitous expletives that are apparently deemed necessary to enliven the narrative, and, hoping that the facts have not been stretched to make a good story, can look forward to instructive entertainment. The author's prologue on the theme of his intense desire to live longer, like the cover advertisement that the book “is for all who want



to stay young as long as they can," should undoubtedly be read with the tongue in the cheek, but what odds to the modern reader, if amusing! Those described are: "Semmelweis: a tragic man afire to find a safe way to help mothers have their babies; Banting: brought new strength to people whose lives were running away in rivers of sugar; Minot: tricked pernicious anemia. Before him it was inexorably fatal; Spencer: found an unprecedented and fantastic way to guard men from spotted fever; Evans: removed one great danger lurking in the American milk supply; McCoy: fighting parrot fever alone, a general who did not want to die in bed; Schaudinn: discovered the pale horror of the sickness which along with cancer is one of humanity's two worst enemies; Bordet: spotted the pale horror's hiding; foretold doom for those neglectful; gave hope to all who'd fight their fate; W. . . . friendly fever, now the electric fever of the new machine. . . . out paresis; Finsen: the Dane who trapped the light of the sun; Rollier: showed the folly of men spending millions to get themselves well when with free Doctor Sun they'd never start to be sick; Strandberg: turned Finsen's machine-sun on TB's most desperate consequence." The author has been able to amplify his sketches by personal contact with nine of the twelve subjects, which gives the reader a sense of closer contact than with the more remote figures of the Microbe Hunters.

E. K.

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SCIENCE AND SUPERSTITION IN THE EIGHTEENTH CENTURY. A Study of the Treatment of Science in Two Encyclopedias of 1725-1750. Study No. 364 in Studies in History, Economics and Public Law, Edited by the Faculty of Political Science of Columbia University. By PHILIP SHORN, PH.D. Pp. 82. New York: Columbia University Press, 1932. Price, \$1.50.

To determine the amount of pseudoscience still clinging to science after the glorious 17th century, the author has examined the way in which science was handled in two representative 18th century encyclopedias—Chambers' Cyclopedia (London, 1728) and Zedler's Universal Lexicon (Leipzig, 1732-1750). Together with Thorndike's similar study of Diderot's Encyclopédie, these constitute "a key to the habits of thought" in science in the three leading countries of Europe. The two encyclopedias are considered separately, necessitating a certain amount of repetition and of division of attention. Thus although the treatment of astronomy by Pythagoras, the Arabians and so forth is considered in Chambers' work, the same has to be taken up again with variations in Zedler's. In medicine, we learn that the work begun by Vesalius and Harvey had had but little influence on scientific thought in overthrowing medieval Galenism—"The two encyclopedias still bear a close resemblance to their earlier medieval prototypes."

E. K.

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ANLEITUNG ZUR FRÜHZEITIGEN ERKENNUNG DER KREBSKRANKHEIT. By various contributors. Pp. 134. Leipzig: S. Hirzel, 1932. Price, Rm. 3-.

This symposium on the early diagnosis of cancer has been written for the use of the general practitioner. It places the responsibility for the successful control of this disease in his hands. The early stigmata of cancer and certain general diagnostic procedures such as the sedimentation time are discussed first. There is next a very detailed review of cancer and sarcoma and its origin from the different epithelial and connective tissues. The larger part of the booklet is devoted to a detailed study of malignancy of every region,

organ and system of the body. Special stress is laid on a few early signs of cancer which should arouse the suspicion of the physician. Naturally the most frequent carcinomata such as carcinoma of the stomach, rectum, cervix and breast receive the most attention. The prognosis, without treatment and with early treatment, and the very earliest and most highly specialized diagnostic procedures are discussed at length. Such a dictum as: "The early diagnosis of malignancy in the small intestines is made by luck, in the large bowel by skill, and in the rectum as a matter of duty" is typical of the many of its phrases. It will be useful in the instruction of both student and general practitioner.

I. R.

ANTONY VAN LEEUWENHOEK AND HIS "LITTLE ANIMALS." By CLIFFORD DOBELL, F.R.S., Protistologist to the Medical Research Council, London; Foreign Member of the R. Accademia dei Lincei, Rome; Sometime Fellow of Trinity College, Cambridge. Pp. 435; illustrated. New York: Harcourt, Brace & Co., 1932.

THIS excellent work—the result of 25 years' personal study—comes opportunely from one of the leading protozoölogists of his day on the 300th anniversary of the birth of the great Dutch microscopist. Finding commentaries more misleading than helpful, the author had chief recourse to Leeuwenhoek's copious correspondence in colloquial Dutch with the Royal Society of London, still extant in their archives. Tedious effort in mastering the difficult script (see Plate 5) as well as the archaic language has revealed much of interest about the man as well as his work that was not previously available. His letters from the first one, sent at the instigation of de Graaf, down to the last, sent on his deathbed a half century later, "contain observations on matters zoölogical, botanical, physical, physiological and miscellaneous (unclassifiable). They are mostly . . . concerned with observations and discoveries made with the microscope."

Following a hundred well-documented pages about Leeuwenhoek's life, methods of work, family relations, contemporary estimates and such like, come two hundred pages of translated letters, with numerous notes and comments. More notes on various personal items, including 27 "lost" letters found by Dobell, are followed by a critical evaluation of Leeuwenhoek's position in science, resulting in the conclusion, which would be hard to controvert, that he is justly regarded as the Father of Protozoölogy and Bacteriology. While the author's notes and comments would in themselves constitute a distinct contribution to the history of science, even more valuable are the original researches and translations now available for the first time. Dobell's successful attempt to preserve the quaintness of the original text, as far as compatible with maintaining the meaning conveyed by their originator, lends further charm to the presentation, still more added to by a strain of old-fashioned humor that pervades the comments and especially the Epistle to the Reader.

E. K.

OFFICE SURGERY. By FENWICK BEEKMAN, M.D., Visiting Surgeon, Bellevue Hospital; Visiting Surgeon, Hospital for the Ruptured and Crippled, etc. (Everyday Practice Series, edited by HARLOW BROOKS, M.D.) Pp. 402; 94 illustrations. Philadelphia: J. B. Lippincott Company, 1932. Price, \$5.00.

THE volumes in this series are prepared primarily for the general practitioner. The cover and format are well done. The author has aptly said

that "there is no such thing as minor surgery for any surgical lesion, be it ever so insignificant, may be the first sign of a serious condition." The form and style in which the subjects have been presented are not strictly conventional, but the author has attempted to "present a readable book." The material for use in an office, anesthesia, wounds, fractures and dislocations, infections, superficial neoplasms and lesions of the external genitalia, anus and rectum are covered in an interesting, terse fashion. The illustrations are good. This volume should prove a valuable addition to the literature of the student and general practitioner.

I. R.

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**FUNCTIONAL DISORDERS OF THE LARGE INTESTINE AND THEIR TREATMENT.** By JACOB BUCKSTEIN, M.D., Instructor in Gastro-intestinal Roentgenology, Cornell University Medical College, etc. Pp. 223; 60 illustrations and 40 reproductions of radiographs. New York: Harper and Brothers, 1932. Price, \$3.00.

THE author has been peculiarly successful in preparing a concise book on the functional disorders of the colon. Our understanding of this organ has been chiefly advanced in recent years by roentgenologic studies and full use of these is made throughout. Detailed instruction in the handling of patients is made to depend whenever possible upon the fundamental pathologic physiology as far as it is understood. Specific information which the practitioner requires is here readily accessible upon such subjects as constipation, enteroptosis, "irritability of the colon associated with mucus," gaseous distension, and the perennial question of chronic appendicitis. The symptoms generally attributed to these conditions are of such great frequency, and the conditions, themselves, so ill-defined, that the experimental approach to their explanation becomes particularly valuable. In the case of the colon, this has been difficult because of the inconsistency of response which characterizes that organ. The experimental data, therefore, are frequently contradictory, and one could wish that even at the expense of compactness the author might more frequently have given his own conclusions from the evidence he presents.

Taken as a whole, the book is well balanced, though one is occasionally surprised, as by the space allotted to studies of such debatable value as the roentgenologic diagnosis of chronic appendicitis. Nevertheless, it is a careful attempt briefly to clarify a very involved field of medicine.

W. O. A.

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**RADIOLOGIC MAXIMS.** By HAROLD SWANBERG, B.Sc., M.D., F.A.C.P., Editor, *The Radiological Review*; Radiologist, St. Mary's Hospital and Blessing Hospitals, Quincy, Ill., etc. With a Foreword by HENRY SCHMITZ, A.M., M.D., LL.D., F.A.C.R., F.A.C.S., Professor of Gynecology and Head of the Department, Loyola University School of Medicine, etc. Pp. 125. Quincy, Ill.: Radiological Review Publishing Company, 1932. Price, \$1.50.

A LITTLE volume devoted to a heterogeneous collection of radiological principles gathered from the rapidly accumulating knowledge of the use of radium and the Roentgen ray. Included are numerous quotations from various medical authorities relative to the value of radiology and the position it now occupies in the realm of medical diagnosis and treatment.

K. K.

MANUALE DI ANALISI CHIMICA. By CESARE SERONO, Dattore in Medicina ed in Chimica; Docente in Chimica e Microscopia Clinica nella R. Università di Roma. In collaboration with PROFESSOR ALFONSO CRUTO. Pp. 483; 85 illustrations. Second edition, Torino: Unione Tipografico-Editrice Torinese, 1932. (Price not given.)

THE outstanding feature and advantage of this manual over similar publications is the general part dealing with elementary chemical procedures, containing data valuable to the laboratory worker. The special part covers complete chemical examination of blood, urine, feces and other excreta and secreta. In addition there are good chapters on food and water analysis, and analysis for the commonest poisons. M. S.

RESEARCHES ON BLACKWATER FEVER IN SOUTHERN RHODESIA. No. 6 of the Memoir Series of The London School of Hygiene and Tropical Medicine. By G. R. ROSS, M.B., CH.B., PH.D., D.P.H., Rhodesian Research Fellow, London School of Hygiene and Tropical Medicine. Pp. 262; illustrated with tables and charts. London: The London School of Hygiene and Tropical Medicine. Price: paper, 8s.; cloth, 10s.6d.

IN his interesting studies Dr. Ross brings out the epidemiology, blood changes, treatment, etc., in patients suffering with blackwater fever. There should not be any fixed outline of treatment, however, as no two cases are alike, and the author is of the opinion that each patient should be treated individually. D. DER.

THE FAILING HEART OF MIDDLE LIFE. By ALBERT S. HYMAN, A.B., M.D., F.A.C.P., Cardiologist, Beth David and Manhattan General Hospitals, etc., and AARON E. PARSONNET, M.D., C.M., F.A.C.P., Attending Physician and Cardiologist, Newark Beth Israel Hospital, etc. With a Preface by DAVID RIESMAN, M.D., Sc.D., F.A.C.P., Professor of Clinical Medicine, University of Pennsylvania School of Medicine. Pp. 538; 166 illustrations, some in colors. Philadelphia: F. A. Davis Company, 1932. Price, \$5.00.

THE authors of this volume have limited themselves almost exclusively to a consideration of those cardiac manifestations that result from a derangement of the blood supply of the heart. The various phases of the subject have been fully and comprehensively discussed. The book is well made up and contains many good illustrations. The style is to be both criticized and commended; it is at times labored and involved and even redundant; but in spite of these handicaps, the book proves easy and pleasant to read.

Many of the conclusions are highly speculative. Some, particularly those based upon a wide application of the theory of functional stenocardia or coronary insufficiency, will not be definitely accepted at the present time by many students of cardiology. However, such hypothetical conceptions do no real harm if they are understood to be tentative; nor do they prevent the book from fulfilling its real purpose. This, as admirably set forth in the preface by Riesman, is to present comprehensively this very important subject to the general practitioner and "to maintain his confidence in himself while at the same time urging him to become acquainted as far as possible with the newer science of cardiology." This aim is well fulfilled.

T. McM.

THE 1932 YEAR BOOK OF RADIOLOGY: DIAGNOSIS. Edited by CHARLES A. WATERS, M.D., Associate in Roentgenology, Johns Hopkins University; Assistant Visiting Roentgenologist, Johns Hopkins Hospital. THERAPEUTICS. Edited by IRA I. KAPLAN, B.Sc., M.D., Director, Division of Cancer, Department of Hospitals, City of New York, etc. Pp. 750; 498 illustrations. Chicago: The Year Book Publishers, Inc., 1932. Price, \$6.00.

In this volume is given a brief review of the principal American and foreign contributions made to radiologic literature during the past year. Of its two parts, the first is devoted to diagnosis and the second to therapy, edited by Drs. Waters and Kaplan, respectively. The authors have succeeded in presenting a concise and comprehensive résumé of the progress made in radiology during the past 12 months. Numerous illustrations and individual references to the original articles add materially to the value of this work. This volume should be appreciatively welcomed by those engaged in the practice of radiology, as it affords an excellent panoramic view of the present status of this specialty. K. K.

THE HISTORY OF DERMATOLOGY. By WILLIAM ALLEN PUSEY, A.M., M.D., LL.D., Professor of Dermatology Emeritus, University of Illinois; sometime President of the American Dermatological Association and of the American Medical Association. Pp. 223; 32 illustrations. Springfield, Ill.: Charles C Thomas, 1933. Price, \$3.00.

THE author, himself an eminent dermatologist, has produced for English speaking readers an account of dermatology that has previously been available only in such works as Puschmann's *Handbuch*, Riehter's *Geschichte der Dermatologie* or in the short introductory chapters of textbooks or scattered through general medical histories. Believing that one should especially study the masters, he has included more than 300 individuals in the 9 chapters that chronologically divide the story of dermatology between 3000 B.C. and modern times. More than half the space is required for the 19th and 20th centuries, however. Though there is considerable space devoted to matters that have little to do with dermatology, this will doubtless not be objected to by the general reader. A novel and most useful feature is a 35-page Historical Index by Dr. Herbert Rattner, which without pretending to absolute completeness gives significant data about skin disease, arranged alphabetically. The book is in Thomas' accustomed high level of bookmaking, excellent paper, type (21 by 38 pica) and binding that makes it a delight to handle. It is, however, no exception to the dictum that the book without an error has never been printed. The illustrations are well chosen and for the most part excellent. E. K.

A GUIDE TO HUMAN PARASITOLOGY. By D. B. BLACKLOCK, M.D. (EDIN.), D.P.H. (LOND.), D.T.M. (LIVER.), Professor of Parasitology, Liverpool School of Tropical Medicine, the University of Liverpool, etc., and T. SOUTHWELL, D.Sc., Ph.D., A.R.C.Sc., F.Z.S., F.R.S.E., Lecturer in Helminthology, School of Tropical Medicine, Liverpool, etc. Pp. 271; 122 illustrations, and 2 colored plates. New York: William Wood & Co., 1932. Price, \$4.00.

This is a well-written, carefully arranged and unusually complete manual. The opening chapters are devoted to discussions of readily available sources

of material for study; simple but practical and accurate means of diagnosis; the mechanics of the microscope, and its care, calibration and use; methods of examining material such as blood, feces and urine for parasitic organisms; and general phases of parasitology and nomenclature. This is followed by sections on spirochetes, protozoa, cestodes, trematodes and nematodes parasitic in man. There is a chapter on myiasis and one giving tabulated summaries of life histories, vehicles of transmission, modes of infection, tissues involved and diagnostic characters. The last hundred pages contain notes on the therapy of parasitic diseases, a list of apparatus and reagents that may be of value, a short list of reference books and an index. The sections dealing with each group of organisms open with general statements, definitions, keys for identification and diagnostic methods. Each organism is discussed with regard to geographic distribution, habitat in the host, morphology, life history, pathogenicity and diagnosis of infection. Tabulated summaries of important facts are given at the end of each section. The illustrations are adequate. The diagrammatic life histories, of which there are 22, should be useful. Practicality is the keynote of the book. It affords a working knowledge of the subject, and is one of the best, if not the best, of its type that has come to the attention of the Reviewer.

H. R.

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**HABITS, THEIR MAKING AND UNMAKING.** By KNIGHT DUNLAP, Professor of Experimental Psychology in the Johns Hopkins University. Pp. 326. New York: Liveright, Inc., 1932. Price, \$3.00.

**MATERIAL** in this work is divided roughly into two sections. The first portion presents the fundamental principles, the theories, the process and conditions of efficient learning. It is very interesting and easy reading and is presented largely from the viewpoint of the laboratory psychologist.

The second section attempts to correlate the earlier material with the breaking of specific bad habits. Bad habits such as stammering, masturbation, tics and homosexuality and other reactions supposedly of psychological origin are used as examples in demonstrating how the breaking of such habits may be carried out through a process of "negative practice," or "unlearning," in other words, a so-called reversal of the learning process.

The author's viewpoint is quite unique and certainly very extreme, and cannot be said to be fundamentally sound; for the detailed discussion of the technique of treatment and associated material does not indicate an unprejudiced knowledge of the deep motivations known to be back of such characteristics or habits. The chapter on the breaking of specific bad habits is particularly full of exaggerations and statements that are not supported by a *wide* "clinical" experience. The great simplification of this work, which is intended for the layman, may be responsible for some of the dogmatic tenor but it does not help an otherwise very novel presentation.

The extensive appendix and bibliography is excellently arranged in direct connection with the material presented in various chapters and can be said to be one of the most valuable portions of the book.

L. S.

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**EXPERIMENTAL ANALYSIS OF DEVELOPMENTS.** By BERNHARD DÜRKEN, Professor in the University of Breslau. Translated by H. G. and A. M. NEWTH. Pp. 288; 120 illustrations. New York: W. W. Norton & Co., 1932. Price, \$4.75.

THE problems and methods of experimental embryology, and some of the results achieved, are here brought together in the form of a survey.

The experimental method in the study of development was used as early as the 18th century, but its modern phase dates from Wilhelm Roux (1850-1924). The material is mostly from the lower vertebrates, especially the amphibians, and from the invertebrates. The subject matter is considered under 8 chapters, such as fertilization and the stimulus to development, the problem of determination, and the influence of environment on the process of development. The number of problems which have already been studied in this comparatively new field is impressive. The details of these are of the greatest interest to the experimentalist and embryologist, but the results and the principles involved have a much wider appeal.

- W. A.

## BOOKS RECEIVED.

### NEW BOOKS.

*A Text-book of Neuropathology.* By ARTHUR WEIL, M.D., Associate Professor of Neurology, Northwestern University Medical School, Chicago. Philadelphia: Lea & Febiger, 1933. Price, \$5.00.

*Urine and Urinalysis.* By LOUIS GERSHENFELD, Ph.M., B.Sc., P.D., Professor of Bacteriology and Hygiene and Director of the Bacteriological and Clinical Chemistry Laboratories at the Philadelphia College of Pharmacy and Science. Pp. 272; 36 illustrations. Philadelphia: Lea & Febiger, 1933. Price, \$2.75.

*Les Rythmes et la Vie.* By MM. LAIGNEL-LAVASTINE, A. M. CHANOT, J. MONCHANIN, G. RICHARD, J. GUITTON, F. MENTRE, H. DUPRAT, H. CARDOT and R. BIOT. Pp. 264. Lyon: Librairie Lavandier, n.d. Price, 15 fr.

*Le Nystagmus Vestibulaire et les Réactions de Mouvements.* By R. CLAUOÛÉ, Professeur libre d'oto-rhino-laryngologie (Bordeaux). Pp. 64; 17 illustrations, 2 in color. Paris: Norbert Maloine, 1933.

*Cervico-vaginitis of Gonococcal Origin in Children.* Report of a Project of The Bellevue-Yorkville Health Demonstration of New York City. By WALTER M. BRUNET, M.D., DORA M. TOLLE, M.D., SARA ALICIA SCUDDER, and ANNE RUTH MEDCALF. Foreword by EMILY D. BARRINGER, M.D., ROBERT L. DICKINSON, M.D., and WILLIAM H. PARK, M.D. Pp. 97; 11 figures, 11 tables and 1 colored plate. New York: Milbank Memorial Fund, 1933.

*El Primer Centenar de Enfermos de Lepra Curados por el Dr. A. Bencheitil.* Pp. 144; 100 illustrations. Bogotá: Editorial Minerva, 1933.

*The Vitamins in Health and Disease.* By BARNETT SURE, Ph.D., Professor of Agricultural Chemistry, University of Arkansas, Fayetteville. Pp. 206; 4 tables. Baltimore: The Williams & Wilkins Company, 1933. Price, \$2.00.

*Fighting Disease With Drugs.* The Story of Pharmacy. A Symposium. Edited by JOHN C. KRANTZ, JR., with an Introduction by DR. JAMES H. BEAL. Pp. 230; illustrated. Baltimore: The Williams & Wilkins Company, 1931. Price, \$2.00.

Collected Reprints from the Laboratories of the Mount Sinai Hospital, New York, 1932. LOUIS GROSS, M.D., Director.

*Ursachen und Behandlung der Krankheiten (causae et curae).* By the Aebtissin Hildegard von Bingen. Translated by PROFESSOR DR. HUGO SCHULZ, Greifswald. Pp. 235. München: Verlag der Aertzlichen Rundschau Otto Gmelin, 1933. Price: Paper, Mk. 10.80; Bound, Mk. 13.

*Studies in the History of Ophthalmology in England Prior to the Year 1800.* By R. RUTSON JAMES, F.R.C.S. (ENG.), Consulting Ophthalmic Surgeon to St. George's Hospital and Senior Editor of the British Journal of Ophthalmology. Pp. 255; 9 plates. New York: The Macmillan Company, 1933. Price, \$4.00.

*Diet in Sinus Infections and Colds.* By EGON V. ULLMANN, M.D., Formerly Special Lecturer for Biology at the Oregon State College; Instructor at the First Medical Clinic at the University of Vienna, etc. Recipes and Menus by ELIZA MEZ. Pp. 166. New York: The Macmillan Company, 1933. Price, \$2.00.

*Medicine in Canada.* Vol. IX of *Clio Medica*. By WILLIAM B. HOWELL, M.D., Anesthetist-in-Charge, Royal Victoria Hospital; Lecturer in Anesthesia, McGill University, Montreal. Pp. 137; 6 illustrations. New York: Paul B. Hoeber, Inc., 1933. Price, \$1.50.

*El Asma Y Otras Enfermedades Alergicas.* By DR. CARLOS JIMENEZ DIAZ. Pp. 945; 88 illustrations, some colored. Madrid: Editorial España, 1932. Price, 60 pesetas.

*The Biochemistry of Medicine.* By A. T. CAMERON, M.A., D.Sc., F.I.C., F.R.S.C., Professor of Biochemistry, Faculty of Medicine, University of Manitoba; Biochemist, Winnipeg General Hospital, and C. R. GILMOUR, M.D., C.M., F.R.C.P. (C.), Professor of Medicine and Clinical Medicine, University of Manitoba; Physician, Winnipeg General Hospital. Pp. 506; 31 illustrations. Baltimore: William Wood & Co., 1933. Price, \$7.25.

*International Clinics.* Vol. II, *Forty-third Series, 1933.* Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, with the collaboration of various contributors. Pp. 314; 31 illustrations, 1 colored. Philadelphia: J. B. Lippincott Company, 1933.

Hyperinsulinism, Pulmonary Hypertension, Stenosis of the Coronary Arteries, the Pathological Physiology of the Circulation, Hypertension, Abnormal Uterine Bleeding, Lymphogranuloma, Standards in Therapeutics, and Recent Progress in Obstetrics and Pediatrics are the subjects discussed in this interesting number.

*The Clinical Aspect of Chronic Poisoning by Aluminum and Its Alloys.* By LEO SPIRA, M.D., with a Foreword by PROFESSOR DR. HANS HORST MEYER, University of Vienna. Pp. 28; 1 illustration. London: John Bale Sons & Danielsson, Ltd., 1933. Price, 2/6.

*Causal Factors in Tuberculosis.* A Report of an Investigation into the Incidence of Tuberculosis in Certain Tyneside Districts. By F. C. S. BRADBURY, M.D., D.P.H., Medical Commissioner of Tyneside Inquiry. Pp. 126; various tables. London: National Association for the Prevention of Tuberculosis, 1933. Price, 2/-.

*The Medical Clinics of North America, Vol. 16, No. 6 (Mayo Clinic Number, May, 1933). Index Number.* Pp. 239; 28 illustrations. Philadelphia: W. B. Saunders Company, 1933.

*A Laboratory Manual of Neuro-anatomy. Part II. Stereographic Plates.* By C. L. DAVIS, M.D., Professor of Anatomy, University of Maryland, and H. S. RUBINSTEIN, B.S., M.D., Instructor in Neuro-anatomy and Assistant in Medicine, University of Maryland. Baltimore: William Wood & Co., 1933. Price, \$3.00.

"This series of stereograms was originally made for use in the teaching of neuro-anatomy at the University of Maryland Medical School. They represent an effort to provide the student at a minimum expense with a satisfactory substitute for the actual specimen. It is designed as an aid to laboratory study of the brain and for bringing to the study an adequate substitute for the specimens usually obtainable in the laboratory alone. Many structures which lend themselves to this method of demonstration are lacking, not because of greater importance of the structures shown but because, in limiting the scope of the work to a point which brings it within the reach of most students, certain structures were arbitrarily selected for demonstration and others omitted." (From authors' Introduction.) Part I, the book itself, will not be ready for publication for a considerable time.



*The Heroic Age of Science.* The Conception, Ideals, and Methods of Science Among the Ancient Greeks. By WILLIAM ARTHUR HEIDEL, Research Professor of the Greek Language and Literature in Wesleyan University; Research Associate of the American Council of Learned Societies of the Carnegie Institution of Washington. Pp. 203. Baltimore: The Williams & Wilkins Company, 1933, for Carnegie Institution of Washington. Price, \$2.50.

*A German Doctor at the Front (Die Front der Ärzte).* By PROFESSOR DR. WILHELM HIS. Translated from the Original German by COLONEL GUSTAVUS M. BLECH, Medical Corps, Reserve, and BRIGADIER-GENERAL JEFFERSON R. KEAN, Medical Corps, U. S. A. (Retired). Pp. 230; 1 illustration. Washington, D. C.: The National Publishing Company, 1933 (American Edition). Price, \$2.50.

*Modern Aspects of Gastro-enterology.* By M. A. ARAFA, M.R.C.P. (LOND.), Medical Assistant to Guy's Hospital, London; Medical Tutor to the Egyptian University and Formerly Senior Medical Registrar to Kasr-el-ainy Hospital, Cairo. With a Foreword by ARTHUR F. HURST, M.D., F.R.C.P., Senior Physician, Guy's Hospital, London. Pp. 374; 79 illustrations. Baltimore: William Wood & Co., 1933. Price, \$8.25.

*Filterable Virus Diseases in Man.* By JOSEPH FINE, M.D., B.Sc., D.P.H. (GLAS.), D.T.M. (LIVERPOOL), Assistant to the Professor of Public Health, Edinburgh University; Formerly Research Assistant, Sir Alfred L. Jones Laboratory (Liverpool School of Tropical Medicine), Freetown, Sierra Leone; Late Assistant Pathologist, Ancoats Hospital, Manchester. Pp. 144. Baltimore: William Wood & Co., 1932. Price, \$2.25.

## NEW EDITIONS.

*Surgical Pathology.* By WILLIAM BOYD, M.D., M.R.C.P. (EDIN.), F.R.C.P. (LOND.), Dipl. Psych., F.R.C.S., Professor of Pathology, University of Manitoba; Pathologist to the Winnipeg General Hospital, Winnipeg, Canada. Pp. 866; 477 illustrations and 13 colored plates. Third edition thoroughly revised. Philadelphia: W. B. Saunders Company, 1933. Price, \$10.00.

This edition retains the excellences of former editions and this is intended as high praise. In addition to extensive alterations, new sections have been added on: metabolism of tumors, the goitrogenous action of cabbage, chronic follicular gastritis, developmental enterogenous cysts, lesions of the appendices epiploicae, Masson's musculonervous complex of the appendix, autolytic peritonitis, cholecystitis glandularis proliferans, high temperature deaths following cholecystectomy, obstruction of the common bile duct, non-obstructive hydronephrosis, injuries to the spleen, bloody discharge from the nipple, Cushing's syndrome, cysts of the semilunar cartilages, and the absorption of bone.

*A Dictionary of Greek and Latin Combining Forms Used in Zoölogical Names.* By EDMUND C. JAEGER, Head of the Department of Zoölogy, Riverside Junior College, Riverside, California. Pp. 157. Second edition. Springfield, Ill.: Charles C Thomas, 1931. Price, \$1.50.

*The Art of Marriage.* A Scientific Treatise. By J. F. HAYDEN, B.Sc. Pp. 218. Revised and enlarged edition. High Point, N. C. Book Sales Agency, 1931. Sales agent: The Union Library Association, New York. Price, 98 cents.

There is no question but that these topics like those of birth control should be available to the intelligent public.

# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

JOHN H. MUSSER, M.D.,

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**The Heart After Diphtheria.**—The well known tendency for occasional involvement of the heart muscle and rare implication of the conduction system during the course of acute diphtheria has raised important questions in reference to this disease causing permanent heart damage. The first serious effort to make a study of the post-diphtheritic heart was made by White and Smith in 1905. Their cases were examined, however, only a comparatively few months after the patients were convalescent from diphtheria. Hoskin has also made an electrocardiographic examination in patients convalescing from the disease, while Jones and White 6 years ago examined 100 patients who had had diphtheria from 5 to 8 years previously. They could find no evidence of organic heart disease in patients who had had diphtheria with that length of time intervening. Sutherland agrees that diphtheria does not have a lasting effect on the heart, whereas Rolleston thinks that it does produce injury and Butler and Levine hold the same view in the instance of heart block. STANLEY ALSTEAD (*Lancet*, 1933, 224, 413) has reinvestigated the whole subject, studying a large number of children who have had diphtheria 1 to 10 years prior to the time of the examination. A considerable number of the cases were excluded for various reasons which might be instrumental in bringing heart changes as a result of some condition other than diphtheria. Ultimately 150 cases were selected for study. The average age of this group was 14 years. There were 21 (14 per cent) who had a history of clinical abnormalities in the heart during diphtheria. Only 2 of these had any symptoms or signs of cardiac lesion on re-examination. Eight patients presented signs and symptoms suggestive of cardiac abnormalities but 2 of these cases were subsequently omitted because the cardiac abnormality was of doubtful importance. In reviewing the brief case reports of these 8 cases it seems that there are 2 or 3 others which might well have been omitted, but aside from that, accepting the author's diagnosis, only 3.3 per cent of the series showed clinical evidence of heart abnormality and, of these, only 2 showed abnormal electrocardiograms. In the group as a whole, the electrocardiograms as contrasted with 100 control cases were virtually the same if such differences as occurred are considered to be caused by chance factors. The only exception to this was that in 90 of the cases of diphtheria there was a negative or isoelectric *T* wave, which abnormality may

or may not mean very much and is of doubtful pathologic significance. The *P-R* interval was remarkably constant. In only 4 instances was there any example of delayed conduction. The *Q-R-S* complex showed a complete absence of any evidence of intraventricular block. The author concludes that "there is nothing to suggest the occurrence of gross cardiac lesions as a result of previous attacks of diphtheria," although he does point out that the abnormalities of the *T* wave in Lead III which are so common in active diphtheria have a tendency to persist long after the disease has subsided.

## SURGERY

UNDER THE CHARGE OF

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**Duodenal Drainage in Gall Bladder Disease.**—About a decade ago there appeared a large number of papers dealing with the use of duodenal drainage in the diagnosis and treatment of disorders of the biliary tract. The interest in this subject was not prompted by new discoveries, but rather by the enthusiasm of individuals who attempted to correlate physiologic principles and clinical methods with diseases of the bile passages. The chief exponent of duodenal drainage for the diagnosis and treatment of disorders of the biliary tract was LYON (*Am. J. Med. Sci.*, 1920, 160, 515), who believed that by the application of the theory of MELTZER (*Ibid.*, 1917, 153, 469) concerning the contrary innervation of the gall bladder, and the sphincter of Gage and Oddi, the gall bladder could be made to empty its contents into the duodenum and that he could collect fractionated specimens of bile from the duodenum. From an examination of these bile fractions Lyon thought that he could differentiate various conditions of the gall bladder and by repeatedly draining the bile from the diseased gall bladder could restore that organ to its normal state. He not only felt that by this method he could determine the presence or absence of pathologic lesions of the biliary tract, but could localize the portion of the tract involved by the mucosal cells found in the material removed from the duodenum.

The objections which arose following Lyon's paper are too voluminous to include in a review. Suffice it to say that these objections dealt chiefly with the ability to cause emptying of the gall bladder, and even if the gall bladder could be made to empty, with the identification of the gall bladder fraction as such. In regard to treatment by duodenal drainage, those opposed to Lyon's method did not believe that it could bring about improvement in the presence of stones or in a viscus whose walls were infected. Unbounded enthusiasm on one hand and extreme skepticism on the other made it difficult to evaluate the

method. In 1924, JONES (*Arch. Int. Med.*, 1924, 34, 60) summarized the controversy thus: "Unquestionably, the early, rather extravagant claims for the method, as a means of diagnosis and treatment, have not been fulfilled. It is also unfortunately true that much of the criticism and pessimism with which the subject is now viewed is due to the claims that have been made by some enthusiasts as regards the efficacy of treatment by duodenal drainage. The undoubted psychologic effect produced by such treatment has undoubtedly been overlooked, or not mentioned by many. On the other hand, the somewhat unequivocal stand of Alvarez and other authors, that the method is without any value, seems equally unjustifiable."

When GRAHAM and COLE (*J. Am. Med. Assn.*, 1924, 82, 613) presented cholecystography as a means of determining the functional state of the gall bladder the question as to the efficacy of duodenal drainage was in doubt and the method was used routinely in but few clinics throughout the country. With the advent of cholecystography other tests for the diagnosis of disorders of the gall bladder became overshadowed. However, in spite of the widespread favorable results with the Graham-Cole test, there were those who, while not agreeing completely with Lyon, felt that the use of duodenal drainage had merit as a diagnostic test. LYON (*Am. J. Med. Sci.*, 1920, 160, 515) depended upon the color and consistency of the gall bladder fraction, the reaction, the microscopic appearance of the cellular debris, and the case with which this dark fraction could be obtained, for his interpretation of the state of the gall bladder and bile ducts.

JONES (*Arch. Int. Med.*, 1924, 34, 60) and PIERSOL, BOCKUS and SHAY (*Am. J. Med. Sci.*, 1928, 175, 84) stated that a study of the sediment obtained after drainage was of the greatest diagnostic import, especially the finding of cholesterol or so-called calcium bilirubinate crystals. During the past year ROUSSELOT and BAUMAN (*J. Am. Med. Assn.*, 1933, 100, 254) and RAFSKY (*Am. J. Med. Sci.*, 1933, 185, 851) have published papers which emphasize anew the advantages of a study of this sediment in the diagnosis of cholelithiasis.

Whether or not the incidence of accurate diagnoses will be higher from a study of the crystallography of the bile obtained from duodenal drainage than from the more commonly used method of GRAHAM and COLE (*J. Am. Med. Assn.*, 1924, 82, 613) cannot be answered from a small series of cases presented from a few clinics. Either method of study requires skill not only in obtaining the necessary data, but in the interpretation of the findings. PIERSOL, BOCKUS and SHAY (*Am. J. Med. Sci.*, 1928, 175, 84), in comparing the two methods, reported correct diagnoses in 88 per cent of cases by means of duodenal drainage as compared with 65 per cent with oral cholecystography. Their results from duodenal drainage are very commendable, but the results from cholecystography seem low. Later, BOCKUS, SHAY, WILLARD and PESSEL (*J. Am. Med. Assn.*, 1931, 96, 311) in an additional study reported that in their hands duodenal drainage gave 98 per cent correct results as compared with 88.4 per cent by cholecystography. However, it appears that with individuals less skilled in duodenal drainage, cholecystography is still the method of choice for the diagnosis of gall bladder disorders.

Since much of the confusion concerning the place of duodenal drainage in the diagnosis of gall bladder disease has resulted from loose

terminology and much theorizing, the use of the term "calcium bilirubinate crystals" for the material which the adherents of the duodenal drainage method believe is characteristic of cholelithiasis is unfortunate, in that it suggests that the identity of the material is as well known as is the entity spoken of as "cholesterol crystals." The fact that this material is colored might suggest the presence of bilirubin, but there is no very plausible reason for stating definitely that the material is the calcium salt of bilirubin.

## THERAPEUTICS

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**The Treatment of Eclampsia and Pre-eclampsia With Thyroxin.**—KÜSTNER (*Klin. Wchnschr.*, 1932, 11, 1016) and others claim that in eclampsia there is an increased activity of the hypophysis, with an increased production of posterior lobe hormone. Although evidence is available that thyroid function is also increased, as a result of the overactivity and antagonistic effect of the posterior lobe pituitary hormone, the balance is dominated by the latter. This concept suggests that the use of thyroxin in eclampsia is rational. The author administered thyroxin in 48 cases of eclampsia. The daily dose varied usually between 2 and 3 mg. by mouth. The total amount administered also showed considerable variations. One patient received 8 mg.; another, 48 mg. In 26 cases, the author claims an improvement due to thyroxin. The improvement manifested itself either in the cessation of convulsions or in decrease of the edema. In 18 cases the improvement was not definite. One patient died. None of the cases with marked improvement had an arterial pressure over 180 mm. Hg systolic pressure; but the edema in this group was usually of marked degree. The group with no improvement, on the other hand, exhibited a relatively higher systolic arterial pressure (180 to 230 mm. Hg) and slight edema only. Cases with pre-eclamptic manifestations showed particularly marked improvement. The author does not advocate thyroxin therapy alone, but states that in some cases it may be of great benefit. Even relatively large doses of thyroxin failed to exert obvious harmful effects on the mother or on the fetus.

**Clinical Experiences With Glucose-insulin Treatment of Cardiac Disease.**—Following the introduction of the therapeutic administration of glucose by Büdigen as a valuable addition to the usual methods of the treatment of cardiac failure, there has more recently been recommended a modification of his plan of therapy in which from 30 to 50 gm. of glucose are given orally or intravenously in the morning fasting state and are followed in from 15 to 20 minutes by a subcu-

tancous dose of 10 to 30 units of insulin. In view of the fact that insulin has been proved to exert harmful effects in the presence of the diseased heart, possibly because of its effect upon glycogen metabolism in the heart, LASCH (*Med. Klin.*, 1932, 28, 1675) studied this procedure in 12 patients suffering from the severest grade of chronic cardiac insufficiency. All 12 were subjected to thoroughly controlled observations which were continued over a considerable length of time. After their response to the prolonged administration of salt-poor diet, digitalis and salyrgan there was added without alteration in their previous treatment the daily administration for 10 days of 50 gm. of grape sugar administered orally and followed after 15 minutes by 10 units of insulin. The author was unable to find any evidence that this addition of sugar and insulin was in any way beneficial to the patient or altered his response to the previous treatment. In some of the cases, moreover, the patient's condition was actually less favorable following than before the administration of the sugar and insulin. The author concludes that this form of therapy for the decompensated cardiac patient is not only valueless but may actually be harmful. He specifically states, however, that this is not to be construed as reflecting upon the therapeutic value of the intravenous use of glucose without insulin.

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**Bichlorid of Mercury Inhalations in the Treatment of Gangrene of the Lung.**—ENGEL (*Deutsch. med. Wchnschr.*, 1932, 58, 1924), having obtained such very satisfactory results from its employment along with other methods in the treatment of gangrene of the lung, seeks to reintroduce the use of inhalations of a vapor of a 1 to 1000 solution of corrosive sublimate. He reports 12 patients so treated in the last few years of whom 4 died, 3 were significantly improved and 5 completely cured. He administers these sublimate inhalations 2 or 3 times daily, spraying in the form of steam a dose of 25 cc. of the solution at each application. He has never seen any unpleasant or harmful effects in spite of sometimes having continued this treatment for 5 or 6 weeks, and there has never been any evidence of mercurial poisoning. He warns that on account of mild irritative conjunctivitis the eyes should be protected from the sublimate spray. The beneficial effects of the treatment usually begin promptly and are first seen in a diminution or disappearance of the putrid odor of the sputum and breath. This is followed by diminution in the amount of sputum and a fall in the temperature. Since the value of arsphenamin and of myrtol are so well established, he combines the administration of these agents with the use of sublimate spray.

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**Work and Insulin in the Management of Diabetic Patients.**—It is established that in milder cases of diabetes moderate or severe muscular exercise usually acts beneficially; the blood sugar falls and the glycosuria may even disappear. In severe cases, on the other hand, there may follow an increased blood sugar content and glycosuria, and acetone bodies may appear. BRAUCH (*Deutsch. Arch. f. klin. Med.*, 1932, 174, 352) reinvestigated this problem with reference to the usual occupational work of the patient and to insulin dosage. For this purpose a comparison was made of the patients' behavior while performing their

usual work in the morning and while resting. These tests were repeated in some of the cases 2 months after the dietetic-insulin-work régime was established. In every case the arrangement followed has considered the individual occupation and character of the diabetes. The response of the patients to muscular work was not uniform. In 3 patients the occupational work resulted in a marked lowering of the blood sugar and urinary sugar elimination. In 7 patients a similar response was observed after moderate work. In 2 patients no difference was noted while at rest or while working. In 1 severe case the work resulted in an aggravation of the condition. The author emphasizes the value of individual gauging of work, diet and insulin.

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## PEDIATRICS

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UNDER THE CHARGE OF  
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**Raw Basic Feeding in the Prevention and Treatment of Dental Caries.**—KUGELMASS and KING (*Arch. Pediat.*, 1933, 50, 307) state that dental caries is a syndrome of many systemic and local disturbances rather than a simple disease of single etiology. Determination of the degree of dental caries was made by means of Bodecker's life caries index in children under continuous supervision for other systemic conditions. Children free from dental caries were of the more stable elements of their race, whose general and mouth hygiene were superior to children with marked dental caries. Dental caries is at its maximum at 6 years for deciduous teeth and at 12 years for permanent teeth, the incidence increasing rapidly with age. This rhythm parallels that of development, thus relating dental caries to deep-seated metabolic changes in the growing body. The degree and prevalence of dental caries was not affected by recurrent mouth and upper respiratory infections. Dental caries is neither prevented nor minimized by breast feeding. Children free from dental caries were maintained in infancy on base-forming dietaries containing early additions of semisolid feeding in the first months of life. Children with moderate and extreme dental caries showed inadequate intakes of vitamins B, C and D. Those maintained on ketogenic diets, base-forming in their mineral content, showed marked dental caries. Those free from dental caries showed consistently a dietary intake excessive in alkali-forming minerals with a preponderance of raw fruits and vegetables. Races immune to dental caries consume sufficient raw alkali-forming fruits and vegetables to balance the acid-forming fresh fish and raw meat.

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**The Relationship of the Rheumatic Process to the Development of Alterations in Tissues.**—COBURN (*Am. J. Dis. Child.*, 1933, 45, 933) says that when the rheumatic subject is infected with the hemolytic streptococcus, the initial response is of the usual character. If the infection is limited to the upper respiratory tract, recovery follows in the course of a few days. This illness, although mild, may be the first

phase in the development of a severe rheumatic attack. Following the subsidence of the local infection, the patient usually regains his usual health, and nothing abnormal is detected clinically. This quiescent stage of days or a few weeks represents the second phase in the evolution of the rheumatic process. This second phase persists until there is a response in the production of immune bodies in the peripheral circulation, whereupon the rheumatic process is activated in susceptible persons. When this occurs, the initial response is characterized by manifestations of a hemorrhagic nature. The most frequent are epistaxis and the erythemas. Melena, hemoptysis and hematemesis also occur. Studies of the excretion of erythrocytes in the urine indicate that there is a very close relationship of hemorrhage to the rheumatic process. Late in the attack, when symptoms are subsiding and abnormal urinary manifestations have disappeared, there may be a second stage, characterized clinically perhaps only by the appearance of subcutaneous nodules. When it was possible to study the tissues of patients dying during the initial stage of a rheumatic attack, hemorrhagic lesions without distinctive histologic character were conspicuous. The appearance of these non-specific lesions suggested the activity of a single process with varying degrees of intensity. This varied from engorgement of the bloodvessels; alteration of the permeability of the vascular tissues with diapedesis, but without demonstrable change in the structure, to inflammatory reaction. The damage to the tissue in the patients with acute rheumatism was characterized by the absence of detectable microorganisms and commonly by vasodilatation, swelling of the endothelium, necrosis of the collagen, infiltration with various wandering cells, and especially hemorrhage. During the first cycle of the rheumatic attack, few or no Aschoff bodies were detected in the cardiac muscle, but the diagnosis was established by the presence of the specific lesions in the endocardium. In this group most of the rheumatic subjects who died survived a long illness with rheumatic fever. In these patients hemorrhage was not conspicuous, and numerous Aschoff bodies were found in the heart muscle. The constant proximity of the Aschoff cells to necrotic collagen in these myocardial nodules suggest the process of healing. The evolution of rheumatic fever consists of three phases. In most instances recognition of the condition clinically is not established until the development of the third phase.

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**Studies in Cretinism and Hypothyroidism: Blood Cholesterol.**—BRONSTEIN (*J. Am. Med. Assn.*, 1933, 100, 1661) undertook this study in order to establish an additional method for regulating thyroid therapy, and so that the clinical course of the thyroid-deficient child might be better understood. It has been shown previously in adults that a relationship existed between hypercholesteremia and hypothyroidism. It was attempted to show that a similar relationship existed in childhood. The blood cholesterol was determined in 25 children in whom no known derangement of cholesterol metabolism was present, and the average was found to be 190+. This value for cholesterol is substantiated by the results of other investigators in this field. Hypercholesteremia was found in the 12 thyroid-deficient children studied. The values ranged from 277 to 782. Thyroid therapy definitely lowered



the blood cholesterol in the cases cited, in addition to raising the basal metabolic rate and effecting clinical improvement. It is desirable to have an additional method for the diagnosing and treating of thyroid-deficient children, particularly in infants and in borderline cases. The use of cholesterol as an aid in the diagnosis and the regulation of therapy offers very satisfactory and definite possibilities.

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## DERMATOLOGY AND SYPHILIS

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**Bacteriologic Studies on Lichen Planus.**—In a disease whose etiology has occasioned much speculation, JACOB and HELMBOLD (*Arch. Dermat. and Syph.*, 1933, 27, 472) present significant evidence for a specific organismal cause. These authors have isolated a Gram-negative, anaërobic, non-motile, non-spore-bearing bacillus from excised lesions in 25 of 28 cases of lichen planus studied. The organism, though somewhat polymorphic, resembles organisms of the colon typhoid type but cannot as yet be definitely classified because of its relatively poor growth. Semisolid dextrose serum agar containing cubes of human tissue was the medium used. The serum must be inactivated at from 56° to 60° C. for a number of hours. The organism was not found in normal skin nor in a number of cases of other papular diseases used as controls. Inoculation of human skin with the organism isolated in a few instances produced lesions which both clinically and histologically resembled lichen planus.

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**Postoperative Gangrenous Ulcer of the Abdominal Wall.**—Increasing interest has been shown in the occasional development of postoperative gangrenous ulcers usually following septic operations on the abdominal cavity, generally in men, and DUEMLING and ELSTON (*Arch. Dermat. and Syph.*, 1933, 27, 624) give an excellent review of the literature, discuss the clinical features, and report an additional case following operation for a ruptured gastric ulcer, with new suggestions for treatment. While authorities vary as to the causative organism, the consensus of opinion points to a streptococcus and a staphylococcus which invades the tissues in symbiotic relationship. This type of progressive gangrenous ulceration usually develops about a drainage opening or stitch hole from 7 to 21 days postoperatively. Most cases follow operations on the gall bladder or intestinal tract in men, rare examples in women even after operation for pelvic inflammatory disease being on record, however. The condition begins as a small, painful, purplish papule which breaks down, ulcerates and spreads in a serpiginous

manner, involving skin, subcutaneous tissue and fascia. In the absence of effective treatment, the process will involve the entire abdominal wall within a period of a few weeks. The authors advocate the use of the infiltration of skin and subcutaneous tissue in advance of the gangrenous process with 5 cc. of bacteriophage (staphylococcus and colon bacillus). This was followed by a general reaction with chill and elevation of temperature to 103° F. in the patient under observation, but repetition of the infiltration at a 5-day interval for 3 times resulted in less systemic reaction and prevented further extension of the process. The authors also recommend the use of oxyquinolin sulphate and scarlet red impregnated gauze originally advocated by Bettman as an epithelial stimulant and for relief from pain attendant on changing dressings.

## GYNECOLOGY AND OBSTETRICS

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**Friedman Pregnancy Test.**—Since the introduction of the Aschheim-Zondek biologic test for pregnancy, there has been considerable interest in work of this sort because of the very high percentage of accuracy. The modification of the test devised by Friedman, in which rabbits are used instead of mice, has been accepted by many investigators on account of certain economic and practical advantages. According to McNEILE and REYNOLDS (*Calif. and West. Med.*, 1933, 38, 1) the Friedman test has an accuracy of about 98 per cent, which parallels that of the Aschheim-Zondek test. It is as yet uncertain as to exactly how soon after conception the reaction becomes positive, probably not under 3 weeks, so that early pregnancy, if negative, should be checked a second time 7 to 10 days later. The test determines the presence of live placental tissue or tissue of placental origin in contact with the maternal circulation. It may, therefore, give false positives in the presence of missed abortions, incomplete abortions or ectopic pregnancies with dead fetal tissue. The reaction might be positive in the case of a macerated fetus as the placenta in these cases frequently contains live tissue. The test is strongly positive in the presence of hydatid mole and chorionepithelioma, and quantitative Aschheim-Zondek tests become an important aid in the diagnosis, treatment and prognosis of these conditions. Primary ovarian failure or castration may cause a compensatory hypertrophy of the anterior lobe of the pituitary gland which may throw an excess of its hormone into the circulation, thus accounting for a certain number of false positive reactions. The technique which they suggest is the injection of 7 cc. of fresh urine on 2 successive days, using a controlled rabbit over 12 weeks of age, killing the animal at 48 hours.

## OPHTHALMOLOGY

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**Ocular Syphilis.**—III. Review of the Literature and Report of a Case of Acute Syphilitic Meningitis and Meningoencephalitis with Special Reference to Papilledema. DRAKE (*Arch. Ophthalm.*, 1933, 9, 234) reports a case of acute syphilitic meningitis and meningoencephalitis in which bilateral choked disks with concentric contraction of the visual fields and limitation of external and downward rotation of the left eye were prominent symptoms. The patient also had occipital headaches, rigidity of the neck, nausea and vomiting, left facial weakness and sluggish pupillary reactions. The Wassermann reactions of both blood and spinal fluid were strongly positive. The spinal fluid contained 227 lymphocytes per cubic millimeter. Under intensive antiluetic treatment, the edema of the disks receded promptly and had completely disappeared in about four months. The vision was considerably improved. Although some authorities believe that acute syphilitic meningitis is always a neurorecidive, only 11 of the 50 cases found in the literature by the authors had had previous antisymphilitic therapy. Of the 30 cases in which examination of the ocular fundus was recorded, 8 showed papillitis, 14 bilateral papilledema, and 2 unilateral papilledema. Argyll-Robertson pupils were present in 7 cases. The Wassermann reaction of the blood was strongly positive in 45 of 48 cases. The Wassermann reaction of the spinal fluid was strongly positive in 49 of the 50 cases. The average cellular content of the spinal fluid was 414 cells per cubic millimeter. The majority of the cells were lymphocytes. Papilledema of syphilitic origin is almost invariably a symptom of acute syphilitic meningitis or meningoencephalitis, which may occur during the secondary stage or more rarely as an acute exacerbation in congenital syphilis, or in a latent period of the tertiary stage. Associated symptoms are headache, nausea and vomiting, coma, delirium or some other mental disturbance, and involvement of other cranial nerves, especially the 3d, 6th, 7th and 8th. The Wassermann reaction of the blood is positive in about 90 per cent of cases, and that of the spinal fluid is always positive. The cerebrospinal fluid is always under increased pressure and contains an increased number of cells. If the Wassermann reaction of the spinal fluid is negative on several successive examinations, the diagnosis of acute syphilitic meningitis is not justified. The prognosis is usually good if antisymphilitic treatment is started promptly. The papilledema usually responds very well to antisymphilitic treatment, but in some cases is followed by postneuritic atrophy. Histologically, acute syphilitic meningitis is characterized primarily by a diffuse, small cell infiltration of the piaarachnoid in which lymphocytes predominate. The infiltration occurs especially around the bloodvessels and extends along them into the brain tissue. The region of the chiasm is often involved in the meningitic process, and the cranial nerves, especially the optic and auditory, are often markedly infiltrated with lymphocytes and plasma cells.

## OTO-RHINO-LARYNGOLOGY

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**The Relationship of Upper Respiratory and Alimentary Tract Flora to Mastoid Infections, With Particular Reference to the Epidemiology of Mastoiditis.**—Wisely employing Holman's method for differentiating and classifying streptococci, KOPETZKY and HADJOPOULOS (*Laryngoscope*, 1933, 42, 661) correlate the bacteriologic findings of cultures made from otitic suppurative lesions with their analyses of certain statistics collected from the records of a general hospital during the sexennium 1926-1931. From an epidemiologic standpoint, it was found that approximately 3 per cent of the total hospital admissions were otologic cases, which seemed to increase in number triennially. The incidence of acute otitic infections reached the peak in March and April; whereas the greatest number of chronic cases occurred in August and September. The mortality curve virtually paralleled that of the chronic infections, and was highest when the general incidence was lowest. The authors believe their studies confirm a phenomenon common to all epidemics—namely, towards the end of the epidemic the ratio of mortality to morbidity shifts in favor of mortality. The general mortality rate was somewhat over 5 per cent, ranging between 8.6 per cent in 1930 and 2.3 per cent in 1931. Unable to explain this fluctuation satisfactorily by data at hand or by merely differentiating the streptococci (which were by far the commonest microorganisms encountered) into the three major groups—hemolytic, green and indifferent—the authors proceeded more minutely to analyze their bacteriologic data. The bacteriologic technique for differentiation and classification of the streptococci was that of Holman, although from the authors' description one gets the impression that the individual strains were not isolated in pure culture before being introduced into the differential fermentation "sets." Moreover, pneumococcus, Type III, is classified as a streptococcus. Hemolytic streptococci were found to be the infecting microbe in about 90 per cent of all cases. *S. pyogenes* accounted for 80 per cent of the cases dying from mastoiditis. *S. infrequens* was associated oftenest with chronic mastoiditis. Study of the annual variations of the streptococcic types in mastoiditis revealed an orderly sequential periodicity, suggesting major cyclic recurrences every 5 or 6 years. According to their findings, indifferent streptococci predominated in 1927 and 1929. *S. infrequens* in 1928, *S. pyogenes* in 1930, and *S. subscidus hemolyticus* in 1931. The authors state that "the existence of such a cyclic change in streptococcic types is borne out by the findings for all other metastatic foci as well as otitic infections." A related paper, "The Prognostic Value of Streptococcic Subculture in Affections of the Ear," was published subsequently by Hadjopoulos in *Laryngoscope*, 1932, 42, 771.

ABSTRACTOR'S NOTE.—Holman's original contribution, "The Classification of Streptococci," appeared in *J. Med. Res.*, 1916, 24, 377, and was abstracted in *Am. J. Med. Sci.*, 1917, 153, 427.

## RADIOLOGY

UNDER THE CHARGE OF

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**d'Arsonvalization in Hyperpiesis.**—In the opinion of HUMPHRIS (*Arch. Phys. Ther., X-ray, Rad.*, 1932, 13, 786) the importance of the d'Arsonval current in its ability to lower a high blood pressure can hardly be overestimated. When there is failing ventricular compensation no attempt should be made to lower the peripheral resistance, but these cases are in the minority. In the great majority of cases the increased tension is due to the imperfect elastic recoil in the arterioles (even with arteriosclerosis) plus increased peripheral resistance, and in these cases the d'Arsonval current acts as a safe specific. The author regards it essential to employ apparatus capable of delivering 2500 ma. by the auto-condensation method.

**A Roentgen Ray Sign in the Diagnosis of Reducible Esophageal Orifice Hernias.**—A roentgenologic sign of reducible hernias at the esophageal orifice is described by CARTY (*Radiology*, 1933, 20, 174). The patient is examined in the vertical, right anterior oblique position, and the ordinary barium mixture is employed. While the breath is held in full inspiration the patient is told to swallow. At that moment the examiner exerts pressure on the anterior abdominal wall with his hand. If a hernia is present the barium stream usually takes an upward course as it is about to enter the stomach. For obvious reasons roentgenographic depiction is usually impracticable, and the observation is essentially roentgenoscopic.

**What Do You Think of Physical Medicine?**—SHAULL (*Arch. Phys. Ther., X-Ray, Rad.*, 1933, 14, 105) points out that it is as difficult to answer this frequently asked question as to answer "What do you think of Radiology?" or "What do you think of internal medicine?" Physical medicine is neither a cult nor a system of healing, and there is no definite line of demarcation between this specialty and surgery or internal medicine. To remove a tumor a surgeon may employ an ordinary scalpel, one heated in a bed of coals, one heated by an electric current, or a cold wire needle with an undamped high frequency current concentrated at its point. In the first two instances the procedures are recognized as surgical; in the last two the operator is perhaps employing physical therapy, although there is no vast difference between any of the methods. In a patient suffering from paresis the internist produces a certain number of temperature elevations by inoculating him with malaria. The physical therapist produces exactly the same number of temperature elevations of exactly the same curve

(if he elects) with diathermy or the hot bath. The results, as far as the paresis is concerned, are quite comparable. It is true that the internist has the malarial parasite and the anemia it has produced to deal with at the end of the series, while the physical therapist has only to turn off his machine or drain his tub. The attempt to evaluate physical medicine as a whole should be abandoned. It is almost as foolish as to attempt to evaluate internal medicine as a whole. In its place the critical evaluation of new appliances and methods of physical therapy by capable men is very badly needed.

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## NEUROLOGY AND PSYCHIATRY

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UNDER THE CHARGE OF

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---

**Psychologic Changes in Normal and Abnormal Individuals Under the Influence of Sodium Amytal.**—LINDERMAN (Am. J. Psychiat., 1932, 11, 1083) feels that sodium amytal produces a marked change in the behavior of certain types of psychotic patients and a less pronounced change in the emotional attitudes of normal individuals, on the basis of the release of inhibitions. It allows the study of the thought content of stuporous patients, which was previously not possible and gives material which can be used in psychotherapeutic efforts.

**Mental Disorders in Siblings.**—HUMM (Am. J. Psychiat., 1932, 12, 239) presents a study of several hundred individuals in order to determine the relative importance of hereditary and environmental factors in persistent criminalism, manic-depressive psychoses, dementia precox, epilepsy and mental deficiency. The individuals consisted of 858 siblings of patients suffering from mental disorders and 214 pairs of twins, one or both of each pair being affected with a mutual disorder. He found that the closer the degree of genetic relationship to an affected subject, the greater the tendency to mental disorder; that some prenatal factor or factors other than heredity play a part in the causation of mental deficiency; that such factor or factors are more frequently operative in twin than in single births; and that this factor or factors are apparently not operative in the other mental disorders studied. He found also that many siblings were affected with disorders dissimilar to those of their respective prepositi. He found a very frequent familial coexistence of epilepsy with migrainous headaches, enuresis and outbursts of rage. In a similar way he found a familial association between manic-depressive psychoses and cases of cycloid personality. The incidence of mutual disorder was greater in the males than in the females, although the female ratio is unquestionably greater in manic-depressive psychoses and in mental deficiency.

## PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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**Contributions to the Pathologic Physiology of Inflammation: The Action of Histamin on Tissue Metabolism.**—Experiments on white mice were carried out by BÜNGELER (*Frankf. Ztschr. f. Path.*, 1932, 44, 1) to determine whether histamin injected into the living animal or allowed to act directly upon fresh tissue *in vitro* would influence the tissue metabolism as determined by the Warburg method. It was shown that the injection of small amounts of histamin corresponding to about one-tenth of the lethal dose brought about a definite increase in the oxygen consumption of the liver tissue; the greatest increase was observed within an hour of the injection (40 to 50 per cent above the normal O<sub>2</sub> consumption) and fell off to normal within 2 or 3 hours. This type of increased metabolism corresponds to that observed by Hess (*Frankf. Ztschr. f. Path.*, 1931, 42, 89), following experimentally induced inflammation of the skin. The author, therefore, believes that the elevation of tissue metabolism observed by Hess was due to the liberation of histamin into the blood stream from the foci of inflammation in the skin. He draws attention to the evidence brought forward by other authors purporting to show the appearance of histamin in anaphylaxis and inflammation and concludes FISCHER-WASELS (*Frankf. Ztschr. f. Path.*, 1931, 42, 1) is correct in his theory that the toxic effects (*Fernwirkungen*) of inflammation are due in part at least to the liberation of products of protein disintegration, chief of which are histamin and allied substances. The injection of large doses of histamin leads on the other hand to a depression of liver metabolism (if the animal is examined in the stage of severe shock). This change of tissue respiration corresponds to that which the author has shown to occur in anaphylactic shock.

**Contributions to the Pathologic Physiology of Inflammation: The Effects of Localized Inflammation on the Reticuloendothelial System as Determined by Vital Staining.**—EICHBAUM and SCHEUFLEER (*Frankf. Ztschr. f. Path.*, 1932, 44, 10) produced extensive subcutaneous inflammation in rabbits by injections of silicious dust (*Kieselguhr*). They then investigated the ability of the reticuloendothelial system to take up vital dyes, and found that the absorption of trypan blue was mildly accelerated about 96 hours after the skin lesions were instigated. With Congo red they found no deviation from the normal. In contrast to the relatively slight effect produced on the reticuloendothelial system by localized inflammation, intravenous injection of milk gave rise to a conspicuous acceleration of the disappearance of Congo red from the blood stream. Subcutaneous injection of milk produced a similar but

more sluggish reaction. Intravenous injection of caseosan markedly accelerated the disappearance of trypan blue from the blood stream, but had no effect on the absorption of Congo red by the reticulo-endothelial system. The authors believe that the rapidity with which vital dyes quit the blood stream is proportional to the phagocytic activity of the reticuloendothelial system and feel justified in concluding that this function of the reticuloendothelial system is mildly increased as a result of localized inflammation, though the increase is small compared to that which can be produced by intravenous injections of foreign proteins.

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**On the Influence of the Vegetative System on the Cholesterin Content of the Blood.**—The few observations made (*e.g.*, in cases of anaphylactic shock, pregnancy, dementia precox) on the influence of the autonomous nervous system on the proportion of cholesterin in the blood indicate that vagotony and hypercholesterinemia are associated with each other. GOEBEL (*J. de phys. et de path. gen.*, 1932, 30, 340) has studied the influence of the vegetative system on the level of cholesterin by pharmacologic methods. He uses a procedure based on the researches of Kraus and Zondek, increasing the quantity of calcium in the organism, and thus causing a temporary displacement of the equilibrium of the electrolytes in the blood in favor of calcium and obtaining excitement of the sympathetic nerve. Dogs were given intravenous administration of 0.2 grains  $\text{CaCl}_2$  in 20 per cent solution per kg. weight, with determinations of the cholesterin in the blood before and at intervals after the injection. This showed that the raising of the tone of the sympathetic nerve by calcium salts brings about hypocholesterinemia. The predominance of the sympathetic nerve was then brought about by paralysis of the parasympathetic by strong doses of atropin (0.005 to 0.01 grains by kg. weight), and it was observed that within 1 hour after administration a diminution of the proportion of cholesterin in the blood was produced. Experiments were then made to study the behavior of cholesterin in the blood during tonic domination of the pneumogastric nerve. The vagus nerve was stimulated by potassium ions (KCl in 10 per cent solution) and then by paralysis of the sympathetic system with ergotamin (the "gynergene" preparation); hypercholesterinemia resulted. The author concludes that the production of cholesterin takes place in the suprarenals, ovaries and spleen, and that the straightening or weakening of the functions of these glands of internal secretion through the nervous system is the cause of the hypercholesterinemia or hypocholesterinemia in the subjects of the experiments.

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**Epithelial Repair in Recovery From Vitamin A Deficiency.**—WOLBACH and HOWE (*J. Exp. Med.*, 1933, 57, 511) have studied minutely and recorded the process of repair of epithelium in recovery from vitamin A deficiency. In their opinion absence of vitamin A causes a starvation specific for many epitheliums. This results in an atrophy and finally in the formation of a stratified keratinizing epithelium regardless of the morphology of the original epithelium. As had been shown previously, this metaplasia is the earliest demonstrable effect of vitamin A deficiency in rats. They found that correcting the vitamin A defi-



ciency in the diet before metaplasia was complete resulted in a rapid restoration of an epithelium identical in morphology with the original epithelium, before the deficiency diet was instituted. In rats in which the process of metaplasia was completed, by keeping the animals on a diet deficient in A for a suitable length of time, they found the process of repair to consist of a vascular degeneration of cells, the upper stratum disappearing by lysis while the lower stratum developed into cells normal for that location. Permanent loss of identity of an epithelium may occur where infection has occurred in cysts or in cases of cicatrized glands. The authors conclude that since the cells of the stratum germinativum preserve the identity of the original epithelium, that this identity is contained within the nuclear chromatin, which is, therefore, unaffected by the deficiency. It is noteworthy that the authors' series of rats were remarkably free of infection, and this gives support to the statement that the condition of vitamin A deficiency does not increase susceptibility to infection by bacteria.

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## HYGIENE AND PUBLIC HEALTH

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UNDER THE CHARGE OF

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**A Study of Tuberculosis Among the Indians in Montana.**—CROUCH (*U. S. Pub. Health Rep.*, 1930, 47, 1907) states that in Montana the death rate from tuberculosis among the Indians is about 15 times as high as among the whites. Among mixed bloods the tuberculosis death rate is much lower than among full-blood Indians. When tuberculin-tested (Mantoux) the figures for positives among children was as follows: Full-blood, 75 per cent; mixed blood,  $\frac{1}{4}$  and more Indian, 54.3 per cent; mixed blood, less than  $\frac{1}{4}$  Indian, 39.3 per cent; whites, 22.6 per cent. Furthermore, it was shown that above the age of 17 years all full-blood Indians tested were positive, while mixed-bloods showed lower figures of positives than in earlier years. The question of race susceptibility is not settled, but it is suggested that complete healing is less frequent in full-blood Indians.

**The Preparation of a Vaccine From Fleas Infected With Endemic Typhus.**—DYER, WORKMAN, RUMREICH and BADGER (*U. S. Pub. Health Rep.*, 1932, 47, 1329) review the preceding work on typhus and Rocky Mountain spotted fever and record the results of their own experiments. Fleas of the species *X. cheopis* infected by feeding on white rats were emulsified and the potency of the emulsion tested on guinea pigs. The virus then was destroyed by the addition of phenol

and used to inoculate guinea pigs. Some protection was shown when the immunized animals were later inoculated with living typhus virus together with a suitable number of control animals.

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**Duration of Viability and Virulence of *Bacillus Pestis*.**—FRANCIS (*U. S. Pub. Health Rep.*, 1932, 47, 1287) subjected a single strain of *B. pestis* to 4 tests of duration of viability and virulence. Pure, undiluted, neutral glycerin at  $-15^{\circ}\text{C}$ . was used for suspending the spleen of a plague guinea pig in one test, while a pure culture of *B. pestis* isolated from the same guinea pig was suspended in glycerin at  $-15^{\circ}\text{C}$ . in another test. The bacilli in the spleen were viable and fully virulent at the end of 7 years, while the glycerinated pure culture was fully virulent for 14 months, slightly virulent for 2 years, 7 months, and dead at the end of 3 years, 5 months. A plain agar culture of *B. pestis* was stored at  $10^{\circ}\text{C}$ ., sealed and unopened, for nine years in 1 test, while in another test a plain agar culture was subcultured every 3 months for 9 years along with other cultures in a general collection of stock cultures stored at  $10^{\circ}\text{C}$ . The result at the end of 9 years was viability and full virulence of the sealed culture, but viability and nonvirulence of the stock culture.

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**The Social Incidence of Rheumatic Heart Disease. A Statistical Study in Yale University Students.**—PAUL and LEDDY (*AM. J. MED. SCI.*, 1932, 184, 597) found the incidence of rheumatic heart disease in a group of 7914 undergraduate students of Yale University to be 8.2 per 1000, as compared with 15 per 1000 which is an average figure obtained from statistics of comparable age groups of individuals in other walks of life. Among the men in this group who had attended expensive boarding schools the incidence was only 5.8 per 1000 as compared with 12.5 per 1000 among those from high-schools. The contention that rheumatic fever is a disease which finds a lower incidence among people of ample means finds support in these observations. According to the methods employed the factor of poverty does not, however, seem to be as important a predisposing rôle in determining the incidence of rheumatic heart disease as it does in clinical tuberculosis.

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**The Prevention of Rickets.**—MITCHELL and COLEY (*J. Am. Med. Assn.*, 1932, 99, 1768) conclude from their studies of a group of 139 babies over a period of 2 years that either cod-liver oil, in doses of 2 or 3 teaspoonfuls daily, or viosterol, in doses of 8 or 10 drops daily, exert a definite influence against the development of rickets, and by either treatment severe or even moderately marked rickets is prevented in babies who live in good hygienic surroundings. In spite of the aforementioned therapy, 22.3 per cent of patients show clinically mild rickets. In 15.9 per cent of the cases the Roentgen findings were positive. The administration of cod-liver oil in the dosage mentioned completely protects 82 per cent of the patients, while the given dose of viosterol completely protects only 75 per cent, in spite of the fact that the amount of viosterol has a little more than twice the amount of vitamin D contained in the daily dose of cod-liver oil. The lowest prevalence of rickets, 9.9 per cent, occurred among those given sunbaths in summer and viosterol or cod-liver oil in winter. The ultra-

violet ray is a satisfactory substitute for sunbaths, the incidence of rickets in those so treated being 13.6 per cent. In the causation of rickets there must be other factors than a deficiency of vitamin D—a comparative deficiency of vitamin A as expressed by De Sanctis and Craig, a deficiency of minerals in the diet as suggested by Weston, or perhaps some other as yet unrecognized agent in which the influence of light possibly plays as important a part as it does in the activation of ergosterol.

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**Oysters and Anemia.**—COULSON, LEVINE and REMINGTON (*Am. J. Pub. Health*, 1932, 22, 1141) report results to show that the oyster is equalled or excelled only by liver in the amounts of iron and copper which it may furnish to the diet in an average serving. That these metals are easily available for hemoglobin production has been shown in previous work in which it was found that oysters, oyster ash (acid soluble) and a solution of iron, copper and manganese in the same quantities, fed to anemic rats, brought about hemoglobin regeneration at the same rate in all 3 cases. Oysters should, therefore, be efficacious in the treatment or prevention of those types of secondary anemia which respond to treatment with iron, or iron plus copper. There is increasing support for the view that dietary deficiencies can best be corrected by proper selection of foods, rather than by the use of artificial concentrates or medicinal mixtures. In order to insure an adequate supply of the inorganic constituents for hemoglobin production it would seem a wise plan also to include oysters in the diet of the pernicious anemia patient in conjunction with liver extract, since it is known that liver extract is relatively low in iron. An average serving of oysters (110 gm.) would furnish about 2 per cent of the human caloric requirement (3000 calories), and yield about 40 per cent of the daily dietary standard for iron, stated by Sherman to be about 15 mg.

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Associate Professor of Neuropathology, Northwestern University Medical School  
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\*A. F. Hurst, British Medical Journal, July 15, 1933, pages 89-94.

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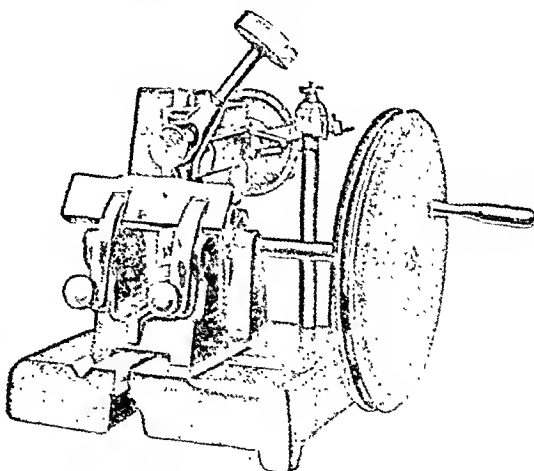
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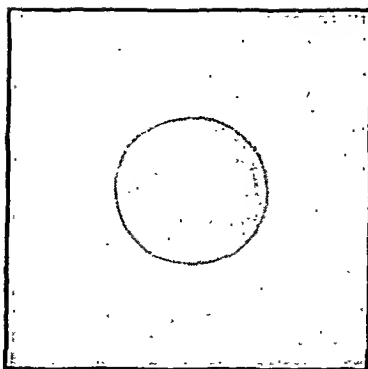


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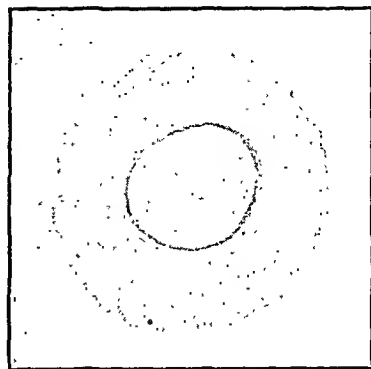
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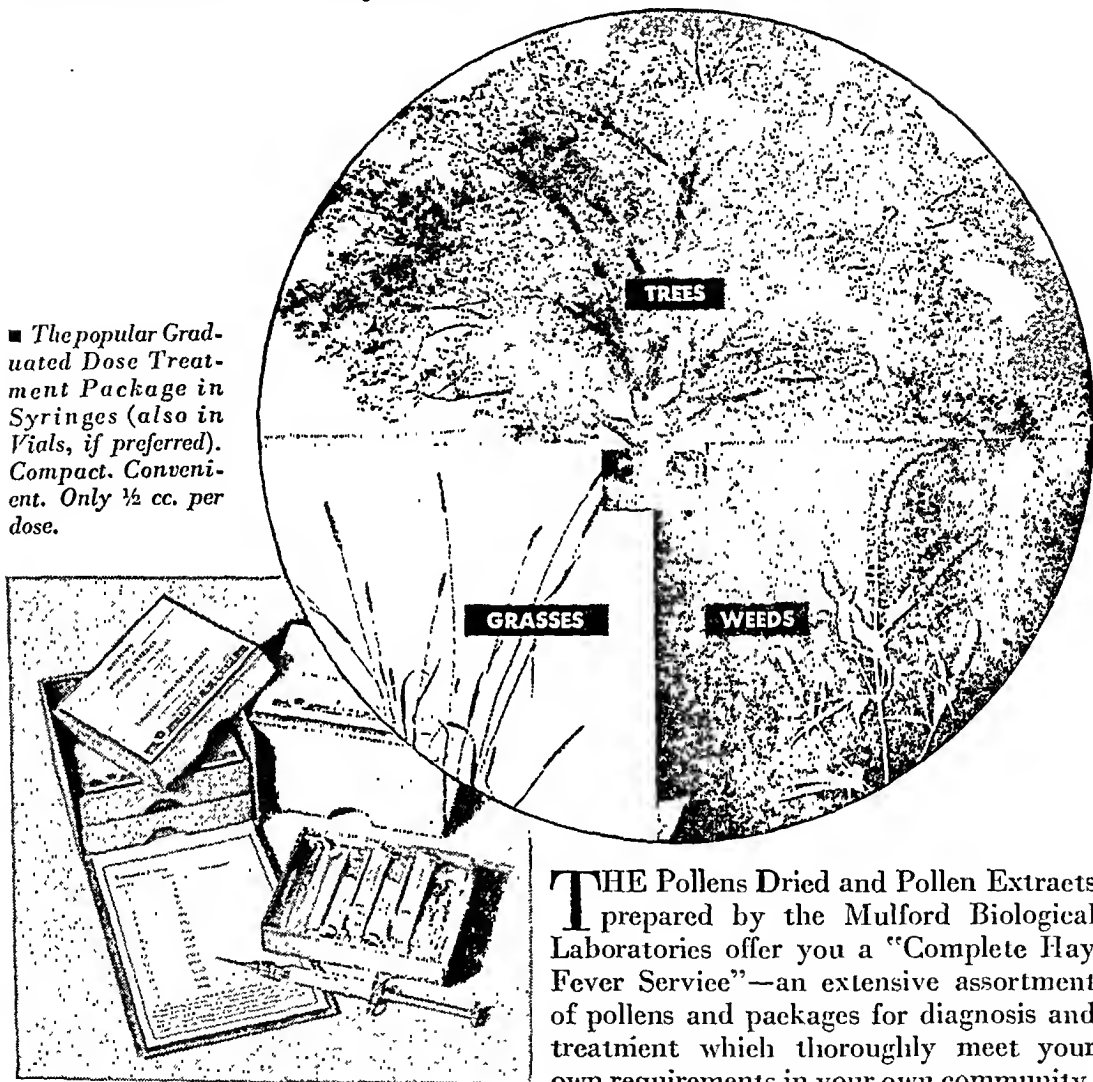
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In discussing the treatment of (decomposition) Feer says: "The period of repair may be shortened by giving suitable additional food; the best, probably, being buttermilk to which carefully regulated proportions of dextrin and maltose preparations or malt soup are added."—E. Feer: *Text-Book of Pediatrics*, J. B. Lippincott Co., Phila., 1922, p. 284.

In the treatment of (infantile atrophy) Fischer recommends the following: "The carbohydrate should be increased by gradual addition of dextrin-maltose.

"Malt soup or dextrin-maltose (Mead's) should be added in teaspoonful or more doses to each feeding until the point of carbohydrate tolerance is reached."—L. Fischer: *Diseases of Infancy and Childhood*, F. A. Davis Co., Phila., 1925, V. 1, p. 285.

Grulec, discussing treatment of (decomposition) observes: "As a rule it is best to start with 2 to 2½ or 3 ounces of albumin milk to the pound weight in 24 hours; the sugar to be added is in the form of a maltose-dextrin mixture. One should never delay too long in adding this."—C. G. Grulec: *Infant Feeding*, W. B. Saunders Co., Phila., 1922, p. 265.

Referring to the (hypotrophic infant) Herrman writes: "In mild cases, the addition of dextrin-maltose instead of cane or milk sugar may be sufficient to obtain a gain in weight."—C. Herrman: *The treatment of nutritional disorders in artificially-fed infants*, New York M. J. 114:158-160, August, 1921.

In discussing artificial feeding in (athrepsia) Hess states: "The carbohydrates are usually added in a slowly fermentable form, such as the maltose and dextrin compounds, which are usually started by the addition of four grams per kilogram (1/15 ounce per pound) and increased until eight grams or more per kilogram (½ ounce per pound) of body weight are added."—J. H. Hess: *Feeding and the Nutritional Disorders in Infancy and Childhood*, F. A. Davis Co., Phila., 1928, p. 278.

Concerning the treatment of (marasmus) Hill says: "When the stools have become smooth and salve-like, carbohydrate, in the form of dextrin-maltose, may be gradually added up to the limit of tolerance."—L. W. Hill: *Practical Infant Feeding*, W. B. Saunders Co., Phila., 1922, p. 281.

"A (spasmodic baby) on bottle feeding should receive a limited amount of milk—a pint, or at the most 24 ounces in the 24 hours—to which cereal gruel and some form of sugar is added, preferably one of the malt dextrin preparations; also the early addition of other foods than milk to the baby's

diet."—M. Jampolis: *Infantile spasmodophilia*, Interstate M. J. 25:652, Sept., 1918; *abst. Arch. Pediat.* 35:691, Nov. 1918.

With reference to the treatment of (diarrhea) Lust writes: "After several days, 2% to 3% of a maltose-dextrin preparation may be added (Dextri-Maltose). This is preferable to the easily fermentable lactose or cane sugar."—F. Lust: *The Treatment of Children's Diseases*, J. P. Lippincott Co., Phila., 1930, p. 145.

"The treatment of artificially fed children in the first of these groups consists in putting them on a low fat dietary, and giving them carbohydrate in the form of one of the less fermentable sugars—e.g., dextrin-maltose."—L. G. Parsons: *(Wasting disorders) of early infancy*, *Lancet*, 1:687-694, April 5, 1924.

Pearson and Wyllie in discussing the treatment of milder cases of (inanition) say: "Regulation of this disturbed organismal balance is obtained by the addition of carbohydrates, while fat and casein are reduced. For this purpose dextrin-maltose and flour are better than the ordinary sugars, since they are more slowly absorbed and have greater efficacy in their powers of controlling the flora in the large intestine."—W. J. Pearson, and W. G. Wyllie: *Recent Advances in Diseases of Children*, P. Blakiston's Son & Co., Phila., 1930, p. 116.

Regarding the treatment of the (marantic infant) Raue states: "After the intolerance to sugar has been overcome a carbohydrate, preferably Dextrin-maltose, may be added."—C. S. Raue: *Diseases of Children*, Boericke & Tafel, Phila., 1922, p. 427.

In discussing the treatment of (atrophy) Thursfield and Paterson, state: "If the baby continues to improve, the next step in the treatment is to add to the milk one of the less fermentable carbohydrates, such as dextrin-maltose; . . ."—H. Thursfield, and D. Paterson: *Diseases of Children*, William Wood & Co., 1929, p. 105.

"I also find dextrin-maltose an excellent addition to albumin-milk when the first object of that food has been achieved and a gain in (weight is desired) in this way I have succeeded in feeding albumin-milk far beyond the period usually advised, with highly gratifying results."—F. L. Wachenheim: *Infant-Feeding; Its Principles and Practice*, Lea & Febiger, Phila., 1915, p. 158.

"Dextri-maltose has been substituted for lactose not infrequently, when the tolerance for the latter continues low."—J. H. West: *Low fat, high starch evaporated milk feeding for the (marasmic baby)*, *Arch. Pediat.* 48:189-193, March, 1931.

"Malt sugar is indicated when others fail to produce a sufficient gain, or when (malassimilation of fat) is evident."—O. H. Wilson: *The role of carbohydrates in infant feeding*, *Southern M. J.* 11:177, March, 1918; *abst. Arch. Pediat.* 35:447, July, 1918.

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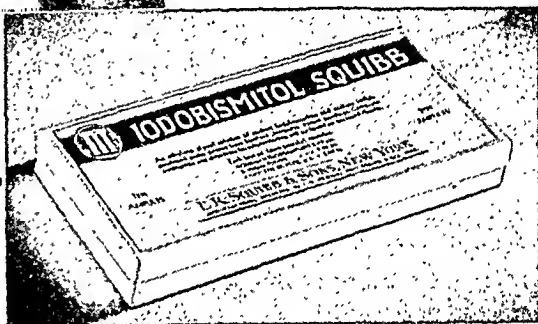


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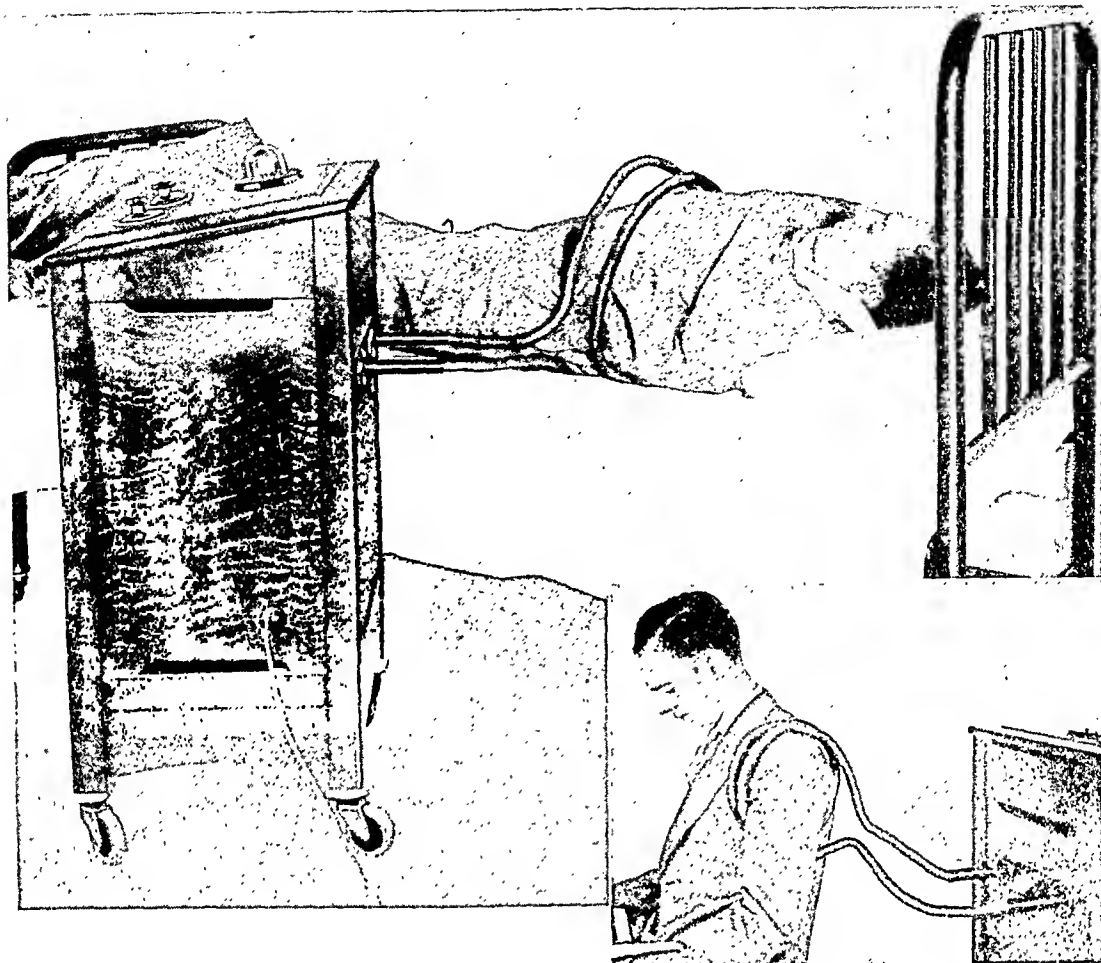
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MARCH, 1934.

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ORIGINAL ARTICLES.

A STUDY OF JAUNDICE IN SYPHILIS.

ITS RELATION TO THERAPY.

By UDO J. WILE, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY,

AND

WILEY M. SAMS, A.B., M.D.,

RESEARCH ASSISTANT IN DERMATOLOGY AND SYPHILOLOGY, UNIVERSITY OF MICHIGAN,  
ANN ARBOR, MICH.

(Studies and contributions from the Department of Dermatology and Syphilology,  
University of Michigan Medical School, service of Dr. Udo J. Wile.)

THE occurrence of jaundice in early syphilis has been reported as a rare complication of the disease since the 16th century, and its appearance with late syphilis of the liver, especially syphilitic cirrhosis, is not uncommon. Shortly after the advent of arsphenamin, jaundice following its administration was reported,<sup>1, 2, 3</sup> but it was not until the World War that icterus began to be a frequent complication. Scott and Pearson<sup>4</sup> reported 39 cases of jaundice out of 2243 patients treated, an incidence of 1.7 per cent, while Pulvermacher<sup>5</sup> reported an incidence of 2.75 per cent over a period of 15 months.

Prior to this time most cases had been thought to be entirely due to the toxic effect of the drug. The advent of epidemics of infectious or so-called "catarrhal" jaundice in the armies, and later in civilian populations, added a problem to the diagnosis, and led some to think that many cases were on the basis of an intercurrent infectious hepatitis. The question of hepatorecurrence, the rôle of heavy metal, the effect of infections in general, and previous liver damage are problems that we have studied in the following groups of patients with jaundice: (a) Untreated cases of jaundice



and syphilis; (b) jaundice following treatment for syphilis with one of the arsphenamins; (c) infectious jaundice; (d) syphilitics who develop jaundice during or after malarial therapy.

The material for the study has been compiled from the records of the University Hospital, covering the period from January 1, 1925, to March 1, 1933. The cases are consecutive, with no attempt at selection.

**Syphilis With Jaundice.** An examination of the hospital records shows that we have seen 10,021 cases of syphilis in the period studied (4.3 per cent of all admissions). These cases were diagnosed as follows:

TABLE 1.—TYPE OF SYPHILIS ENCOUNTERED.		No. of cases.
Latent . . . . .		5,460
Central nervous system . . . . .		1,680
Active (primary and secondary) . . . . .		1,065
Congenital . . . . .		1,040
Cardiac . . . . .		385
All other types . . . . .		391
Total . . . . .		10,021

In this entire group the diagnosis of syphilis of the liver was made either clinically, following operation, or at autopsy in 91 cases, a percentage incidence of 0.9. This includes all types of hepatic syphilis and is, in our opinion, a low figure, not representing the true incidence of liver syphilis. In fact, it is difficult to see how any organ as vascular as the liver can escape involvement early, or not show evidence of syphilis later upon postmortem examination. Many are definitely occult, as proven by postmortem examination.<sup>6</sup> Inadequate knowledge of liver physiology, the absence of a satisfactory test for hepatic function, the large margin of hepatic reserve, and the known regenerative ability of the liver combine in making a diagnosis of syphilis of the liver difficult. Tests of hepatic function have been discussed in detail by O'Leary, Green and Rowntree.<sup>7</sup> In brief, we must rely upon disturbance of biliary or glycogenic function, change in size of the liver or a disturbance of portal circulation for the clinical diagnosis. These give us evidence of liver damage only when the process is extensive.

The types of cases of hepatic syphilis are shown in Table 2.

TABLE 2.—TYPES OF SYPHILIS OF THE LIVER ENCOUNTERED.		No. of cases.
Early hepatitis:		
Icterus gravis . . . . .		0
Benign . . . . .		5
Chronic hepatitis:		
Diffuse interstitial . . . . .		65
Gummous . . . . .		10
Cirrhosis—all types . . . . .		9
Banti's syndrome with syphilis . . . . .		2
Total . . . . .		91

Of the 5 cases of hepatitis in active secondary syphilis, only 2 were jaundiced, and 1 of these had a septic infection following a recent abortion. In both cases the jaundice responded fairly promptly to heavy metal therapy. The other 3 cases, with enlarged firm livers, were given initial heavy metal therapy and did not develop jaundice subsequently. In 2 cases it was noted that the liver returned to normal size.

Of 65 cases of diffuse interstitial hepatitis, in 7 the diagnosis was made only at autopsy. Serologic tests were taken on but 4 of these and were positive in only 1 who had congenital syphilis. Of the remaining 58, the diagnosis rests upon a firm and palpable liver associated with other signs of syphilis. Only 1 of these cases later came to autopsy with confirmation of the diagnosis microscopically. In this group, only 3 cases had a clinical icterus. In 1 case the diagnosis was not confirmed by further studies. In a second the surgical department favored a diagnosis of obstructive jaundice; the exact cause was not determined. The third case responded to specific therapy. Two others had elevated blood bilirubins, 8 and 10 mg. per 1000 cc. respectively, but no clinical icterus. They were treated with mercury and iodids at the time and did not subsequently develop jaundice.

In the group of cases with gummosis hepatitis, 1 had deep jaundice, fading rapidly after administration of mercury and potassium iodid; a second gave a definite history of transient jaundice shortly before, but could not be further studied. Only 1 case came to autopsy and the diagnosis of gummosis hepatitis was confirmed.

In the group diagnosed as syphilitic cirrhosis, 6 cases had physical signs of portal obstruction and 2 of these also were slightly jaundiced; 2 others presented jaundice without portal obstruction; in 1, a patient with congenital syphilis—not jaundiced—a postmortem diagnosis of Hanot's cirrhosis was made; in 4, the diagnosis was confirmed by autopsy. Two patients have been treated specifically, with apparent good results.

There were 2 cases with Banti's syndrome with syphilis, both showing some response to antiluetic therapy. One relapsed when specific treatment was withdrawn and again improved when it was resumed.

In all, then, of the 91 cases of hepatic syphilis, only 13 had clinical jaundice, 2 had slightly elevated blood bilirubins only, and 1 gave a definite history of recent jaundice. None of these 16 had ever received antiluetic therapy before admission to the clinic. Our incidence of jaundice with hepatic syphilis is thus 17 per cent. In 2 cases the question of "catarrhal jaundice" was raised, and it might be added that 2 additional cases of syphilis with supposedly catarrhal or infectious jaundice were excluded in our subsequent group of infectious hepatitis. Since our purpose is to establish the frequency of pre-therapeutic jaundice, we will count them here.

Our incidence of jaundice then before treatment is 0.18 per cent (18 in 10,021 cases). This is lower than Werner's<sup>8</sup> report of an incidence of 0.37 per cent in 15,799 cases of early syphilis, while Goldstein<sup>9</sup> found 20 in 7462 patients with early syphilis (0.26 per cent). We found but 2 cases of jaundice in 1065 early cases of syphilis (incidence of 0.18 per cent).

**Post-arsphenamin Jaundice.** Statistics on the frequency of jaundice in syphilis following treatment with one of the arsenobenzenes presents a strikingly different picture. Of the 10,021 cases of syphilis examined in the clinic during the period, only 4126 were treated in our clinic with one of the arsphenamins. The remainder were sent back to their home physicians for treatment or for various reasons were treated with heavy metals and iodids or plasmodium therapy. Our patients received a total of 35,936 treatments and 56 developed jaundice (1.35 per cent). A comparison with other reports shows this to be about average. For example, Harrison<sup>10</sup> had an incidence of 0.6 per cent; Gaston and Poutoiseau,<sup>11</sup> in 1600 patients, 0.76 per cent; Stokes, Ruedemann and Lemon,<sup>12</sup> in 5200 patients, 1.3 per cent. On the other hand, Scott and Pearson<sup>4</sup> reported 1.7 per cent; Pulvermacher,<sup>5</sup> 2.75 per cent; Friedmann,<sup>13</sup> nearly 3 per cent; Clément-Simon and Vulliémoz,<sup>14</sup> in 1100 patients, 5 per cent. In our groups, then, post-arsphenamin jaundice is 7.5 times as frequent as pre-therapeutic jaundice.

The material on which this part of our study is based consists of 65 consecutive cases of jaundice following one of the arsenobenzene preparations. The group ranged in age from 10 to 58 years (average, 30.6). There were 26 women and 39 men, or 1 to 1.5, while in the treated group the women outnumbered men by 1.27 to 1. The duration of the syphilitic infection ranged from a few weeks in early cases to periods of 15 to 25 years in late cases. All types of syphilis were represented, and in 3 of the cases treated elsewhere syphilis was proven to be non-existent. At the time treatment was instituted, 7 patients had only a primary lesion, 12 had developed secondary manifestations, 22 were latent, 14 had central nervous system syphilis, 2 had aortitis, and 5 had congenital syphilis. The greatest interest attaches as to which type of arsphenamin is the most hepatotoxic. (Table 3.)

TABLE 3.—INCIDENCE OF JAUNDICE ACCORDING TO DRUG AND METHOD OF TREATMENT.

	No. of cases treated.	No. of cases jaundice.	Percentage incidence.
Tryparsamid . . . . .	279	3	1.07
Neoarsphenamin . . . . .	921	7	0.76
Arsphenamin . . . . .	2926	46	1.57
Non-intensively (weekly) . . . . .	563	10	1.77
Semi-intensively (3 in 10 days) . . . . .	363	5	1.39
Intensively (3 in 3 days) . . . . .	2000	31	1.55
Totals . . . . .	4126	56*	1.35

\* Nine other cases came to hospital because of jaundice following arsenobenzene. All treated by neoarsphenamin.

It will be noticed that arsphenamin, calculated on a percentage basis, produces twice as many cases of jaundice as neoarsphenamin. This, however, probably does not indicate that neoarsphenamin is less hepatotoxic, as most of the patients treated with this drug are babies and children with congenital syphilis, in which group we had no case of post-arsphenamin jaundice below the age of 10 years. Moreover, all the outside cases entering the hospital for jaundice had received neoarsphenamin. It will also be noted that the intensive method of administering arsphenamin (3 treatments in 3 days) has not produced a greater percentage of jaundice than the less intensive methods. We also found no relation between the severity of the jaundice or its duration and the amount of drug given. That impurities or a deteriorated drug could be responsible in many cases does not seem likely when the cases are well distributed over several years. Obviously, however, such a complex unstable drug might contain impurities and be responsible in a few cases. (See Wilcox.<sup>15</sup>) In 1928 we changed, following a fatal case of arsphenamin jaundice, to the preparations of another firm, since when we have had no fatal cases from jaundice, but we have had more cases.

Cases of post-arsphenamin jaundice can definitely be separated into early and late types. In the early cases the jaundice may follow treatment in from 1 to 15 days. Clément-Simon and Vulliémot<sup>14</sup> have reported the earliest case, which came on immediately following the first injection which had caused a nitritoid crisis. In our series, 18 are early cases (average, 6.5 days from last intravenous treatment).

The causes ascribed to early icterus may be listed as follows: (1) Herxheimer reactions. (2) Toxic reactions: (a) due to overdosage; (b) due to hypersusceptibility or idiosyncrasy.

The first of these conditions, the Jarisch-Herxheimer reaction, or "reaction de foyer" of the French, has long been recognized as a cause of early benign and fairly transient jaundice. The mechanism is due to a sudden destruction of spirochetes in the liver and elsewhere, with a liberation of syphilotoxin and subsequent damage to the liver. Two of our early cases we feel were the result of this phenomenon. They came on within 24 hours after the first injection in patients who had early syphilis but had had no previous treatment. The jaundice was mild and lasted but 4 or 5 days. Later the patients were again placed on an arsphenamin, without further trouble.

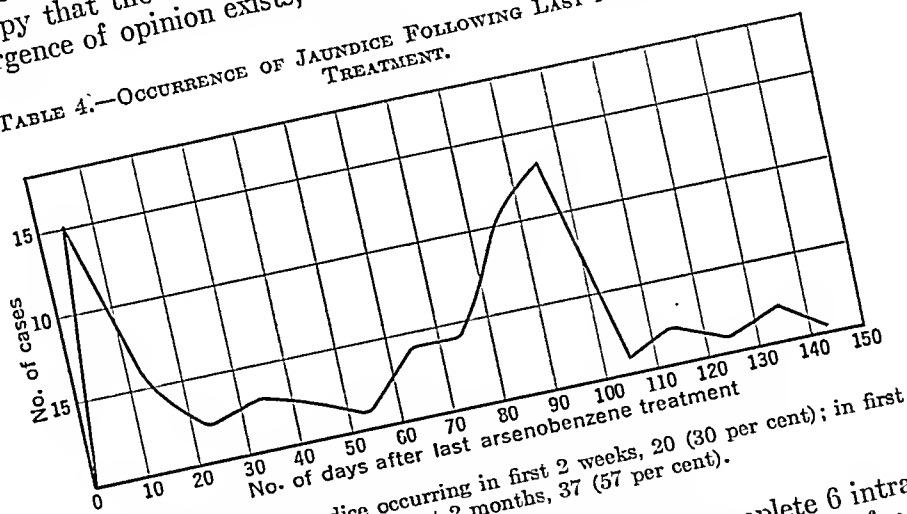
Excessive dosage can, we feel, be responsible for but 1 of our cases. The patient, a man, aged 58, was given a pre-operative course of 2 neoarsphenamin treatments in our clinic. Upon discharge from the hospital he received at the hands of another physician 16 intravenous injections of neoarsphenamin, given twice a week. Jaundice followed the last injection by 3 days. Although this patient also had avertin anesthesia and was a chronic alcoholic,

we feel that he also received an excessive amount of neoarsphenamin for his age and condition.

In the remaining 15 early cases the dosage of drug was not excessive and was less than that ordinarily given. The average number of treatments was 2.6 per patient. In this group in all cases there are initial signs of toxicity which followed the administration of the drug immediately or within a few hours. Most commonly this consists in a febrile reaction, frequently initiated by a chill and accompanied by a marked gastro-intestinal reaction which may last for several days. A third of these cases developed a toxic erythema which subsided as the jaundice appeared. There is then a very definite trend of events leading from the time of treatment up to the onset of jaundice. That this is the result of a toxic reaction from arsphenamin is self-evident.

**Late Post-arsphenamin Jaundice.** It is in late icterus following therapy that the difficulty in diagnosis obtains. Here the widest divergence of opinion exists, and it is in this group that a majority

TABLE 4.—OCCURRENCE OF JAUNDICE FOLLOWING LAST ARSENOBENZENE TREATMENT.



Number of cases of jaundice occurring in first 2 weeks, 20 (30 per cent); in first 2 months, 28 (43 per cent); after first 2 months, 37 (57 per cent).

of our cases fall. On the average, these patients complete 6 intravenous treatments and have been discharged on heavy metal for a period of 3 months. It is just at the time when they are due to continue their third course of intravenous treatment that their jaundice appears. Table 3 shows the rise of this second or late peak of jaundice; nearly  $\frac{2}{3}$  of our cases occur at this period. On the average, it occurs 80 days after the last intravenous treatment, the height of the curve falling at 96 days. Our longest delayed case is 139 days.

There are three major theories as to the cause of the late icterus: (1) Delayed toxic action of arsphenamin on the liver; (2) a hepato-recurrence; and (3) an intercurrent infection, usually in the nature

of a so-called catarrhal jaundice. Numerous other factors have been emphasized by various investigators at least as contributing elements: heavy metals, alcohol, malaria, pregnancy and many others.

The delayed toxic action theory, which was at first the favorite, has some evidential support. Table 3 shows that there is a fairly definite silent period of about 3 months after administration of the drug. This interval, which we can refer to as the "latent period of jaundice," is well marked and is noted both in our series and in those of other clinics.<sup>12, 16</sup> Todd<sup>17</sup> reported an average latent period of 10 weeks. He also reported that further administration of neoarsphenamin had a deleterious effect upon the course of the jaundice and concluded, therefore, that the drug was a causative factor. Against this view we can summon certain experimental evidence, namely, the frequent failure to produce arsphenamin jaundice in laboratory animals, even with definitely toxic doses.<sup>20</sup>

Certain investigators have reported that arsenic is retained in the liver for months.<sup>18, 19</sup> Silbergleit and Föckler,<sup>20</sup> on the other hand, were unable to show arsenic in the liver of 2 fatal cases, nor could they demonstrate arsenic in the excretions. Lynch and Hoge<sup>21</sup> likewise failed to demonstrate arsenic in 3 fatal cases. Most clinicians have been unable to find arsenic in the urine and hair of the late jaundice cases. A majority of our determinations have been negative, and 2 of 3 positive tests were obtained within 1 week of the last treatment. One of our late cases gave a positive test for arsenic 104 days after the last treatment. No studies of arsenic in feces of jaundice patients have been made. The greatest variations in opinions exist as to the duration of arsenic retention and excretion following arsphenamin. (See Vogel.<sup>22</sup>) Milian<sup>23</sup> found, in a patient dying from syphilitic meningitis after 3 injections of arsphenamin, that the lungs and spleen contain several times more arsenic in proportion to their weight than the liver, indicating that the liver is not a site of election.

It is incontestable, however, that arsenic jaundice is much more frequent than jaundice in the population as a whole. Ruge<sup>24</sup> found jaundice to occur 16 times more frequently among the personnel of the German Navy treated with salvarsan than among the rest of the Navy—an excellent control as the two groups lived under the same environment. Without doubt arsphenamin plays a major part in the production of the late jaundice, but the exact mechanism of its action is not clear. The ability of patients again to tolerate arsphenamin after recovery from a late jaundice is well known, and 16 per cent of our patients later continued arsenobenzene therapy either in our clinic or elsewhere without a single recurrence of jaundice. There must be, then, some immediate factor which precipitates the hepatitis.

The rôle of syphilis as a cause of the late jaundice has long been

championed by Milian,<sup>25</sup> who advanced the theory that in 90 per cent or more of the late cases the jaundice was the result of a recurrence of syphilis in the liver. In other words, it was a hepato-recurrence comparable to mucocutaneous relapse and the well-known neurorecurrence. He based his opinion on the time interval which occurs between the last injection of the drug and the onset of the jaundice, noted the case as being due to short and inadequate treatment, and recommended further intensive treatment with arsphenamin. Of 75 cases so treated, 60 had good results, 11 were intolerant to arsenobenzenes, and there were 4 deaths. The duration of the jaundice was shortened to 10 or 15 days, according to his reports. This latter fact has not been observed in other clinics when arsphenamin has been given.

Let us enumerate first the evidence favoring hepatorecurrence: (1) The time interval between the last arsenobenzene and the onset of jaundice tends to average about 3 months, and this corresponds with a period in which neurorecurrence or mucocutaneous relapse may occur. (2) Patients frequently discontinue their heavy metal therapy during this period and are predisposed to relapse. (3) Administration of further arsphenamin during the jaundice has not resulted in any severe exacerbation of the jaundice or symptoms, and frequently causes no difficulty; this would be unusual if arsphenamin were the cause of the liver dysfunction. (4) Late icterus is infrequently accompanied by symptoms of arsphenamin intoxication. (5) Finally, Milian frequently finds concomitant evidence of active syphilis and a high percentage of positive serologic reactions. Others have reported jaundice associated with recurrent secondary lesions.<sup>27</sup>

As opposed to this view, the following facts stand out: (1) In 42 cases of late jaundice there was not a single case of mucocutaneous relapse or neurorecurrence, yet a recent survey indicates that with early syphilis we have about 4 per cent neurorecurrences during the first year of treatment. (2) Only 14 of the 45 jaundice cases had had active syphilis, 15 cases were purely latent, 12 had central nervous system syphilis, 2 congenital syphilis, and 1 had aortitis. In these latter groups an active relapse would be unusual. (3) Twenty-five of the patients had 6 or more 2-grain injections of bismuth subsalicylate or 40 mercury rubs following the last arsphenamin injection, 18 patients had less than this amount, and only 2 had no heavy metal therapy during the interval. All of the patients had received bismuth injections along with the intravenous therapy. We believe this adequate to prevent relapse in most cases. (4) The serologic reaction remained unchanged in 19 patients of the group, 11 patients did not have serologic study, 7 patients had serologic tests during the time of jaundice and only 2 were positive. Eight other patients had a negative serologic reaction after the jaundice. There were no reversals from negative to positive with the onset of

jaundice. (5) Five cases in whom slight jaundice was present, but not noted, returned to the clinic and were inadvertently placed on arsphenamin. Of this group following the next arsenical treatment, 1 patient died in 5 days, the only death from treatment on our service during the period studied. The other 4 recovered from their jaundice in an average of 23 days. This recovery in 4 of the cases is not sufficient evidence to justify a diagnosis of syphilitic jaundice. We feel that they recovered in spite of the treatment rather than because of it. (6) In this controversy it is of greatest significance to note that no known form of liver syphilis is commonly characterized by icterus and in our 91 cases of hepatic syphilis only 16 were jaundiced.

The third major problem in this discussion concerns itself with the differentiation of delayed post-arsphenamin jaundice from jaundice due to infectious hepatitis. The latter is often termed epidemic jaundice when it occurs in large numbers, or "catarrhal" jaundice when it occurs sporadically. This type of jaundice has always been common in troops during wars. A marked increase was noted during the latter part of the World War and in the following years epidemics were reported in Europe and North America. Stokes, Ruedemann and Lemon<sup>12</sup> noted an increase in their post-arsphenamin jaundice simultaneously with an epidemic of jaundice in southern Minnesota. More recently Ruge has published a series of statistical articles on the incidence of post-arsphenamin and infectious jaundice in the German Navy.<sup>24, 27</sup> In support of this view the strongest point is the almost complete inability in any given case to make the differential diagnosis between infectious and toxic hepatitis. As an aid in study of this phase of the condition, we have taken 69 consecutive cases of infectious jaundice which occurred during a similar period. They represent sporadic cases of infectious hepatitis and they vary more in their symptoms and physical findings than is the case where the infection occurs in epidemic form.

The patients in this group range in age from 1 to 60 years, the greatest number falling in the second and third decades, and the average age being 25 years. There were 25 female and 44 male patients. Six cases of post-arsphenamin jaundice were found diagnosed "catarrhal" jaundice and 2 cases of untreated syphilis with jaundice were found in the group. These, together with those cases which were later found to have stone or cholecystitis, were excluded for the purposes of comparison with our post-arsphenamin group. Surgical cases were likewise excluded in the post-arsphenamin group. Milian, in a recent article,<sup>23</sup> claims that quiescent angiocholitis and cholelithiasis are often stirred into activity by anti-luetic treatment. We have not gained this impression.

The average number of treatments with arsphenamin or similar drug in the late jaundice is 6 injections, and the highest total



dosage given in 6 treatments was 3.6 gm., while for the average the total dosage was 2.4 gm. With neoarsphenamin the figures are similar. The patients did not develop any immediate reaction of severity nor have any previous difficulty until the onset of jaundice. This lack of toxic symptoms at the onset favors the opinion that other causes than arsphenamin play the immediate rôle in the production of the late icterus. The average case has its onset at about the time when the patient is due to return for continuation of arsphenamin therapy. It frequently follows an upper respiratory infection or gastro-intestinal upset, after which the patient feels ill and in many of the cases nausea and vomiting ensue. The appetite becomes poor, there is a loss of weight, and a lack of energy. Then, in about 6 to 8 days his friends notice he is becoming jaundiced. Usually by the time he returns to the clinic the jaundice is well marked, but the patient is feeling somewhat better. Under treatment in the hospital the jaundice usually lasts a month, fading very slowly. Table 5 compares the symptoms in our post-arsphenamin and infectious groups.

TABLE 5.—COMPARISON OF SYMPTOMS IN POST-ARSPHENAMIN AND INFECTIOUS JAUNDICE.

	Post-arsphenamin jaundice, per cent.	Infectious jaundice, per cent.
Nausea . . . . .	47.1	47.8
Vomiting . . . . .	45.2	39.1
Asymptomatic . . . . .	24.5	7.3
Pain or soreness of abdomen . . . . .	20.7	34.3
Upper respiratory infection . . . . .	20.7	18.9
Fever . . . . .	17.0	21.7
Anorexia . . . . .	17.0	39.1
Indigestion, distress, "gas," etc. . . . .	13.2	34.3
Chills . . . . .	11.3	8.7
Pains in back or extremities . . . . .	9.4	8.7
Pruritus . . . . .	9.4	8.7
Constipation . . . . .	7.5	26.0
Diarrhea . . . . .	7.5	1.4
Malaise, weakness . . . . .	5.6	31.8
Headaches . . . . .	1.9	13.0
Epistaxis . . . . .	1.9	1.4

The essential differences noted between the two groups are: (1) Asymptomatic onset and course are more common in the post-arsphenamin group. (2) Pain or tenderness in the abdomen is a bit more common in the infectious group, as are headache, malaise and weakness. (3) Constipation is more common and diarrhea uncommon in the infectious group. (4) Indigestion and loss of appetite are more common also in the infectious group. Other writers have pointed out that the patient with therapeutic jaundice is a sicker patient than with infectious jaundice, a point that our experience does not cover. Other than the evident icterus, which is of varying degree, the most significant physical finding in both groups is a palpable liver. The liver is more commonly tender in

infectious jaundice, while a palpable spleen is a bit more common in the post-arsphenamin group.

TABLE 6.—PHYSICAL FINDINGS IN POST-ARSPHENAMIN AND INFECTIOUS JAUNDICE.

	Post-arsphenamin jaundice, per cent.	Infectious jaundice, per cent.
Palpable liver . . . . .	60.0	53.6
Liver tenderness . . . . .	13.7	26.1
Palpable liver and spleen . . . . .	11.6	5.8
Excoriations . . . . .	0	2.9

Although certain differences in the two groups are evident, it is, nevertheless, apparent that in any given case it is quite impossible to differentiate between them. Numerous studies have been made on the two conditions with the purpose of aiding in a differential diagnosis, but material differences are not consistently found. Stool and urine examinations or a history of clay-colored stool or dark urine gave results which were approximately the same. The findings depend more upon the time, severity and duration of the jaundice than upon any other factor. Leucin and tyrosin crystals were found in the urine of a patient who died with acute yellow atrophy and in another patient who subsequently recovered.

Several investigators have studied the blood findings and arrived at opposite opinions as to their value in differential diagnosis and significance. Ruge<sup>28</sup> has studied his cases and concluded that there is no difference between the blood counts in post-arsphenamin and infectious jaundice. He found in both conditions an early mild leukocytosis with an increase in neutrophils which soon gives way to a mild leukopenia with a lymphocytosis and mononucleosis. With Schilling counts there was no shift to the right or left. Thewlis and Middleton<sup>29</sup> had previously reported leukopenia as "an almost constant blood finding in uncomplicated catarrhal cholangitis." Polymorphonuclear cells were depressed more than the other white blood cells, and the large mononuclear cells show a slight increase. They further reported the depression to be in direct ratio to the severity of the disease and that in the average case the blood returns to normal in about 2 weeks. Still earlier, Jones and Minot<sup>30</sup> reported a transient and minor leukocytosis and a constant absolute lymphocytosis even when leukopenia was present. Lerman<sup>16</sup> studied a group of 50 cases of arsphenamin jaundice statistically and concluded that "arsphenamin jaundice was characterized by a slight leukocytosis and a normal differential count in contradistinction to the characteristic leukopenia with relative lymphocytosis that develops in catarrhal jaundice." Furthermore, the total leukocyte count in arsphenamin jaundice tends to be higher during the first week of jaundice than thereafter.

Compiling the reports from our blood counts, we have the results indicated in Table 7. This method in arriving at an average blood

picture has many sources of error and it is not surprising that different investigations have resulted in a wide divergence of opinion. We are struck by the wide range of variation in the total leukocyte counts and in the differential pictures and were unable to correlate these findings either with the day of the disease or its severity.

TABLE 7.—RESULTS OF BLOOD STUDIES IN INFECTIOUS AND POST-ARSPHENAMIN JAUNDICE.

	Infectious jaundice.	Post-arsphenamin jaundice.
Average leukocyte count before onset of jaundice . .	5715 (60 per cent poly- morphonuclear cells)	6550 (71 per cent poly- morphonuclear cells).
Average leukocyte count after onset of jaundice . .	8357 (61 per cent poly- morphonuclear cells)	7066 (61 per cent poly- morphonuclear cells).

NOTE.—The period before onset of jaundice varied from 1 to 11 days in the two groups and the period after jaundice varies from 1 to 54 days. They represent, therefore, early and late periods respectively in the duration of the disease.

In our opinion, the blood study will not aid in the differential diagnosis. Blumer<sup>31</sup> has stated that the blood picture of infectious jaundice is not characteristic but variable. With this opinion we are in entire accord, and we feel that this is equally true in the group of post-arsphenamin cases. There is to date no satisfactory clinical or laboratory method of distinguishing between certain cases of post-arsphenamin jaundice and others of infectious jaundice.

Table 8 shows a tendency for the late post-arsphenamin jaundice cases to be slightly more common during the winter months, but this is not so marked as with infectious jaundice. This tendency has been previously noted by others. Todd,<sup>17</sup> reporting a series of cases which occurred during the World War, found that the greatest majority of his cases started with the onset of cold weather.

TABLE 8.—COMPARING INFECTIOUS AND POST-ARSPHENAMIN JAUNDICE ACCORDING TO MONTHLY OCCURRENCE.

<i>Infectious Jaundice (69 Cases).</i>												
Jan. 4	Feb. 7	Mar. 6	April. 4	May. 2	June. 6	July. 4	Aug. 4	Sept. 5	Oct. 9	Nov. 8	Dec. 10	
<i>Late Post-arsphenamin Jaundice (45 Cases).</i>												
7	7	2	2	4	1	3	3	4	3	4	5	

In Table 9, comparing yearly incidence of post-arsphenamin and infectious jaundice, it can be pointed out that nearly 60 per

TABLE 9.—YEARLY OCCURRENCE OF INFECTIOUS AND POST-ARSPHENAMIN JAUNDICE FROM 1925 TO 1933.

<i>Infectious Jaundice (69 Cases).</i>									
1925. 4	1926. 8	1927. 12	1928. 4	1929. 10	1930. 11	1931. 14	1932. 8	1933.* 0	
<i>Late Post-arsphenamin Jaundice (45 Cases).</i>									
1	3	4	6	3	5	13	8	2	

\* January and February only.

cent of our late post-arsphenamin jaundice cases occurred during the years of 1930, 1931 and 1932. At the same time, just a few (less than half) of the cases of infectious jaundice were treated in the hospital. An even greater tendency for such a grouping has been reported by writers who have studied the problem during an epidemic of acute infectious jaundice (Ruge, Stokes and others).

These figures we feel are of some significance in spite of the fact that the groups studied are not well controlled. If post-arsphenamin jaundice were identical with infectious jaundice, we would expect the incidence to be similar, and we would have but 6 instead of 45 late cases. It is evident, then, that too much significance cannot be placed on the above comparison. In a review of the occurrence of infectious jaundice in the student group of the University, the rate per M averaged 1.55 over the period of 8 years, from 1925 to 1933. In the student group, cases of infectious hepatitis varied from 2 in 1928-1929 to 24 in 1932-1933, with an average enrollment of 8000.<sup>33</sup>

Other possible contributing factors can be considered. What part does heavy metal therapy play? Ruge<sup>24</sup> found only a few cases following the administration of bismuth alone, but he does not state how many cases have been so treated. In the opinion of Silbergleit and Föckler,<sup>20</sup> who reported 13 fatal cases, the simultaneous administration of the heavy metal with arsphenamin is much more productive of serious accidents. Strathey, Smith and Hannah<sup>33</sup> offer the same opinion. In our experience, neither bismuth nor mercury alone have produced toxic jaundice, and it has long been our practice to limit the treatment of cardiac and hepatic cases of syphilis to heavy metals and iodids, and not to treat with the arsphenamins patients over the age of 50 years who have only latent syphilis, except in a few cases. We have given or advised such treatment in a large number of individuals with never a case of toxic jaundice. We are consequently of the opinion that the heavy metals are not especially hepatotoxic, but this, of course, does not prove that they do not play a contributing rôle. We have 6 cases in our late jaundice group who developed a stomatitis after using mercury rubs before the onset of their toxic hepatitis. There were no cases with diarrhea or renal damage from mercury in this group. Furthermore, none of our patients who have had a nephrosis from mercury has subsequently developed jaundice. We have had no untoward reactions with bismuth. One patient, a non-syphilitic with a phagedenic ulceration of the penis, was treated elsewhere with a series of 50 injections of bismuth antimony tartrate and later was given 2 injections of neoarsphenamin. He developed a jaundice 7 days after the last intravenous injection and entered the University Hospital for treatment. Keefer<sup>34</sup> has reported toxic jaundice following the administration of antimony preparations.

Several writers, during and immediately following the World

War, believed that the increased incidence of jaundice at that time was the result of a very limited diet which predisposed the liver to damage by arsphenamin. We do not consider that such a factor applies in our cases. A considerable number believe that a high carbohydrate intake spares the liver and they recommend such a diet for the treatment of toxic hepatitis.

We believe, however, that the condition of the organ does play an important rôle in the production of the jaundice either of the early or late type. That the syphilitic infection itself imposes some load upon the organ cannot be denied. In any systemic infection it must be called upon in some respect in protecting the organism and eliminating the endogenous toxins. Rehder and Beckman<sup>35</sup> have stressed the point that the stage of infection with syphilis is important and that jaundice is more common with a florid secondary syphilis of some months' duration, and less common in early primary cases and late central nervous system syphilis. They point out that jaundice is not a common complication of antisypilitic therapy in psychopathic institutions where late or old cases of syphilis predominate. Zimmern<sup>36</sup> is also of this opinion and in his collected cases jaundice occurred in early syphilis 218 times as compared with 88 cases in late syphilis. Our records do not bear out this contention directly—19 of our cases were either in the primary or secondary stage, 22 were purely latent, 14 had nervous system syphilis, and 5 were cases of congenital syphilis.

Other evidence of recent or concurrent liver damage is indicated in Table 10. One-third of the cases had, in addition to the syphilis and the arsphenamin, other causes which may have contributed to the failure of liver function.

TABLE 10.—EVIDENCE OF PREVIOUS LIVER DAMAGE IN 65 CASES OF POST-ARSPHENAMIN JAUNDICE.

	Cases.	Percentage incidence.
Hepatic disease . . . . .	9	13.8
Specific hepatitis . . . . .	3	
Gall-bladder disease . . . . .	4	
Previous jaundice . . . . .	2	
Malaria . . . . .	4	6.1
Recent pregnancy . . . . .	4	6.1
Recent general anesthesia (Avertin-ethylene-ether)	3	4.6
Alcoholism . . . . .	2 (?)	3.1
Percentage of patients with evidence of previous liver damage . . . . .		33.7

The data in Table 10 constitute only presumptive evidence of liver damage, which in the absence of satisfactory tests for liver function is as yet unproved. This, of course, does not include any estimate of occult syphilis of the liver: in all cases where syphilis existed, some damage may have been done.

Intercurrent infection other than infectious hepatitis probably plays some part in the production of jaundice. Kecfer<sup>34</sup> is of the

opinion that streptococcal infection may produce profound anatomic changes in the liver and account for a jaundice in patients with streptococcus septicemia. Upper respiratory infections were noted in the records of 13 of our patients, oral sepsis in 20, otitis media, sinusitis or tonsillitis in 10 more, mercurial stomatitis in 6, and a severe pyelitis in 1.

In addition to infections, 3 of the group had had a general anesthesia following the course of antiluetic therapy. Jaundice and acute yellow atrophy of the liver following chloroform are not rare. This has been the subject of experiment by McJunkin,<sup>37</sup> who reported experimental failure to damage the liver of animals with arsphenamin after it had already been affected by chloroform. Jaundice following both avertin and ether have been reported.

The part played by pregnancy and by alcoholism is still more difficult to evaluate, but since both are known to cause liver damage under certain conditions they cannot be considered as of no consequence. Alcoholism has been singled out as a contributing factor in producing the jaundice by several who have commented on the subject. A history of alcoholism was obtained in but 2 of our cases.

**Jaundice in Therapeutic Malaria.** Since jaundice not infrequently occurs during or shortly following malarial therapy in syphilitic patients, we have reviewed these cases in the hope that it might throw some light upon our problem. That jaundice occurs as a complication of malaria has long been recognized, and Clifford<sup>38</sup> states that malaria always damages the liver, sometimes fatally. Cirrhosis of the liver with pigment formation in chronic malaria forms one of the classic pictures in human pathology,<sup>39</sup> even though it is uncommon. James, Nicol and Schute<sup>40</sup> record jaundice as a very frequent complication of induced malignant malaria using *P. falciparum*.

We have treated 322 patients with plasmodium therapy for syphilis of the central nervous system of various types. Out of this number, 7 (2.14 per cent) developed jaundice. Only 1 of these patients had previously had a jaundice following arsphenamin. In this patient the course, symptoms and severity of the jaundice were almost identical during both attacks. We have had 5 other cases of post-arsphenamin jaundice who subsequently were treated with malaria and who did not develop icterus.

Three of the patients in this group of 7 had never had arsenobenzene therapy of any type and 3 had had recent treatment. In 1 case the interval following the last intravenous treatment was just 76 days, the same as the average in our late type of cases. Two patients who received malarial therapy before arsphenamin treatment developed jaundice during their initial course of arsphenamin. We can draw no conclusions except that combined malaria and arsphenamin, both exerting a toxic action on the liver, lead to a jaundice more frequently than either agent alone. There is nothing characteristic in the course of jaundice in malaria which

aids in differentiating it from infectious or toxic icterus. The van den Bergh reaction is indirect when the bilirubin is lower than 20 mg. per 1000 cc. and direct usually when above this figure. Few fragility tests have been made. Anemia has with some strains of the plasmodium been severe enough to warrant cessation of the paroxysms. At other times the hemoglobin and red blood cell count have remained higher than the appearance of the patient would indicate. We agree with the opinion expressed by O'Leary, Green and Rowntree,<sup>7</sup> that hemolytic crises may in part explain the jaundice of mild degree, but that when severe there is an element of hepatic injury. Until this hepatic damage occurs, the blood bilirubin, although elevated, does not usually produce a clinical jaundice.

During the past few years we have made blood bilirubin determinations on all of our jaundice cases about every third or fourth day. The van den Bergh reaction, as pointed out above, varied with the quantity of bilirubin, almost always being direct when the bilirubin was high and indirect when low, that is, below 20 mg. per 1000 cc. One case with Banti's syndrome gave biphasic reactions with a reading as high as 42 mg. per 1000 cc. The highest bilirubin obtained in the infectious jaundice group was 120 mg. per 1000 cc. and the duration of jaundice in this case was 28 days, with recovery. The highest reading in the post-arsphenamin group was 100 mg. per 1000 cc. and the patient recovered in 31 days. In general, when the blood bilirubin is higher than 50 mg. the duration of the jaundice is longer than a month and often 2 months. The jaundice recedes slowly and this is said to be indicative of widespread liver damage. When the jaundice does not become intense, and the blood bilirubin is but 20 to 25 mg. per 1000 cc., the duration is from 1 to 3 weeks. There is considerable variation in this matter. In our 2 fatal cases the highest readings were 70 and 94 mg. per 1000 cc. Noticeable variations in the depth of jaundice are accompanied by a corresponding rise or fall in the bilirubin reading. At the onset the bilirubin content of the blood rises faster than the depth of the icterus would indicate, while later the icteric tint may not fade as rapidly as the bilirubin content of the blood falls.

Milian<sup>23</sup> reported positive blood reactions in his late cases, while others have reported an unusual number of negative serologic reactions. Rehder and Beckman<sup>35</sup> reported that 20 of their patients had negative serologic reactions before the onset of icterus, and during the period of jaundice he had only 3 with positive reactions, and these 3 patients did not subsequently show serologic reversal. Strathey, Smith and Hannah<sup>33</sup> reported 8 fatal cases and 39 non-fatal cases in which all but 2 gave a negative Wassermann reaction before their jaundice cleared up. Todd<sup>17</sup> found a negative Wassermann in all 24 of his cases during jaundice. In the last two groups the patients were British troops and all were cases of early syphilis. In our cases with both early and late jaundice covering both

recent and old syphilis, we were also struck with the unusually high percentage of reversal of the serologic test from positive to negative. We consider this unusual in view of the relatively small amount of specific therapy—2 to 8 treatments—and the short period which elapsed from the start of treatment, averaging but 3 months. Of 65 cases, 57 were serologically positive on admission to the hospital, and 40 of these had further serologic study. Thirteen had blood tests during the period of jaundice; 3 of these had become negative, 4 were less strongly positive and 6 remained unchanged. Of 33 cases which have returned to the clinic, 18 are still positive while 15 have been persistently negative. Of the 15 cases showing reversal, 8 were of early syphilis, 4 were purely latent cases, and 3 had central nervous system syphilis. None of these patients have again become positive and several of them have been followed for 6 years. Of those in whom there were no change from positive to negative, 3 were cases of early syphilis, 5 were latent, 2 had aortitis, 7 had central nervous system syphilis, and 1 had congenital syphilis. A more comprehensive study of the cases in which serologic reversal occurred will be reported in a later paper.

We had only 2 fatal cases and 1 of these had not received his treatment at our hands. We have had, then, but 1 death from toxic hepatitis in 4126 cases. The patient treated elsewhere received neoarsphenamin of a dosage not known. He had received several previous treatments with no apparent trouble. When after a period of 6 months he resumed treatment, he was sick following the injection and developed jaundice on the 11th day. He died 36 days later with toxic nephritis and a terminal bronchopneumonia. The liver had shrunk in size before death and post-mortem examination showed acute yellow atrophy of the liver. The second patient was treated with arsphenamin and had received 8 treatments, with a total dosage of 3.35 gm. As has been pointed out above, the patient was given more arsphenamin at a time when he had bile in his blood. This patient's jaundice evidently was the result of a previous course of treatment which had been completed 91 days before. He became markedly icteric, irrational, then comatose and died within 5 days. The autopsy examination showed acute yellow atrophy of the liver. This experience leads us to advise strongly against the use of any arsphenamin preparation in patients with jaundice. If there is any evidence suggesting hepatorecurrence, heavy metal treatment would be the method of choice.

**Summary.** The subject of post-therapeutic jaundice as seen in our clinic during the past 8 years had been discussed. A review of several groups of patients was made with particular reference to the incidence of infectious jaundice and of other associated factors which, together with the type of treatment administered, could have led to liver damage. An analysis has been made with reference to the frequency of icterus following arsenobenzene and associated heavy metal therapy. This group was further studied with



reference to the type of arsenobenzene drug employed and an effort to determine their relative hepatotoxicity made. Studies have been made as to the incidence of icterus occurring as a manifestation of syphilis in cases in which arsenobenzene had not been employed. This was undertaken for the purpose of comparison with the post-therapeutic group and tends to incriminate the arsphenamins as factors in the production of jaundice. Symptomatology and physical findings have been studied in an endeavor to determine, if possible, the pathognomonic criteria for post-arsphenamin jaundice.

**Conclusions.** 1. Jaundice following the use of arsenobenzenes in the treatment of syphilis is a not infrequent complication, and its relative incidence in our series and in those reported by others indicates that a high degree of hepatotoxicity is exerted by the drugs.

2. The low incidence of jaundice in untreated syphilis, 0.18 per cent, as compared with a percentage of 1.37 following arsphenamin, further incriminates these drugs as factors.

3. It is not believed that post-therapeutic jaundice can be regarded as a hepatorecurrence, as is stated by Milian.

4. The symptomatology and the physical findings of the late or delayed type of post-therapeutic jaundice so closely approach those of infectious or so-called catarrhal jaundice as to make differential diagnosis possible only upon the history. The blood findings are not constant or characteristic.

5. A possible relation of post-arsphenamin jaundice to the incidence of infectious jaundice, as pointed out by Stokes, Ruedemann and Lemon, is to some extent borne out by our studies.

6. About 60 per cent of the cases of post-therapeutic jaundice occurred in a period of 3 years, during which time almost half of the cases of infectious jaundice studied for comparison also occurred.

7. Extraneous associated factors exerting hepatotoxicity, such as pregnancy, malaria and alcoholism, play a minor rôle.

8. The pathologic diagnosis of acute yellow atrophy in 2 fatal cases studied, as well as others reported in the literature, indicate that the icterus results from a severe intoxication and destruction of the liver substance analogous to other forms of poisoning leading to acute yellow atrophy.

9. Until more accurate means are at hand to determine susceptibility and liver function, and until the drug is modified to make it less hepatotoxic, post-arsphenamin jaundice will continue to be among the severe complications of the modern treatment of syphilis.

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## THERAPEUTIC PNEUMOTHORAX IN EXPERIMENTAL LOBAR PNEUMONIA IN DOGS.\*

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THERAPEUTIC pneumothorax on the affected side in lobar pneumonia has been used by Continental clinicians since 1921, when

\* The experimental work was conducted in the Laboratory of Surgical Research and the Pepper Laboratory of Clinical Medicine, University of Pennsylvania School of Medicine. This study was aided by a grant from the Faculty Research Committee, University of Pennsylvania.

Friedmann<sup>1</sup> reported on its use in 7 patients. He found that when artificial pneumothorax was instituted on the affected side severe pain subsided and respirations became quiet, with evident improvement in the general condition. In these and David's<sup>2</sup> 6 cases all patients recovered without complications. Schottky<sup>3</sup> (1923) reported using the procedure once "as a last resort" on the 5th day of the disease with excellent results and prompt convalescence. Ibrahim and Duken<sup>4</sup> (1928) used it in 3 infants with pneumonia with recovery; and Duken<sup>5</sup> later successfully treated 5 other children with pneumonia by this method. Jahr and Neumann<sup>6</sup> also reported 5 cases of lobar pneumonia in infants successfully treated. The cases reported by Ibrahim and Duken, and Duken, as well as one reported by Jahr and Neumann, were treated late in the disease (12th to 35th day); here the treatment must be regarded as being given for a complication of lobar pneumonia rather than for the acute pneumonia itself. In 1931, Taylor<sup>7</sup> used artificial pneumothorax in the treatment of pleurisy in pneumonia in 3 cases, with immediate relief of pain. In 1932, Coghlan<sup>8</sup> used it in 6 cases of lobar pneumonia with complete recovery in 5. In the 1 fatal case, an attempt was made to produce an immediate and complete crisis because of the desperate condition of the patient; 750 cc. of air was injected at one time, a very violent crisis set in, the patient perspired freely and cyanosis became markedly diminished. A few hours later the pulse began to rise and signs of failure of the right ventricle appeared, the patient dying the next day. He says "the fatality in this case can be attributed to an error in judgment in a difficult situation and lack of knowledge of the technique, owing to inexperience, rather than to a defect in the method of treatment itself, for it was obvious that the pneumonic process was as well controlled by the artificial pneumothorax in this instance as in the other cases."

Coghlan's work has stimulated others to use this form of therapy and in the past year Hanau<sup>9</sup> and Guadarrama<sup>10</sup> have commented favorably on its uses in lobar pneumonia and the latter has published 1 case. Li<sup>11</sup> reported 6 cases from China with one fatality in a case that also had an effusion in the right pleural cavity. After the injection of air there was marked improvement in the patient's condition. Four days later the fluid increased with consequent displacement of the heart to the left, death occurring on the 4th day. Anderson<sup>12</sup> reported 3 cases with complete recovery. Perlroth and Topercer<sup>13</sup> treated 7 patients with one death. The fatality occurred in a chronic alcoholic with confluent bronchopneumonia and jaundice. We know of no cases in the American literature.

The number of published cases totals 50. Their ages range from 6 weeks to 62 years. In 41, the day of the disease on which therapeutic pneumothorax was instituted ranged from the second to the tenth. In the remainder, the treatment was begun so late in the disease that it must be looked upon as treatment for a postpneumonic complication. The average number of treatments in each case was two

TABLE 1.—DATA OF REPORTED LOBAR PNEUMONIA CASES TREATED WITH PNEUMOTHORAX.

Author.	Cases.	Ages.	Involvement.	Average days of disease.	Average number of treatments.	Average amount of air.	Result.
Friedmann (1921) . . . .	7	20-39	L. L. L. (6); R. L. L. (1)	2.9	1.4	370 cc. (60-500)	All recovered.
David (1931) . . . .	6	4-39	R. L. L. (2); L. L. L. (1); R. Side (1); R. U. L. (2)	5	...	.....	All recovered.
Schottky (1923) . . . .	1	4½	L. L. L.	5	1.0	400 cc.	Recovered.
Ibrahim and Duken (1928)	3	10 mos.	R. U. L. (3); R. M. L. (1)	16	2.6	270 cc. (100-400)	All recovered.
Duken (1930) . . . .	5	36 mos.	R. U. L. (2); L. L. L. (1); R. Side (1)	22	6.0	250 cc. (150-350)	All recovered.
Jahr and Neumann (1930)	5	8 wks.-2 yrs.	R. U. L. (3); L. L. L. (1); R. Side (1)	7	...	.....	All recovered.
Coghlan (1932) . . . .	6	6 wks.-6 mos.	R. M. L. (2); R. U. L. (1); R. L. L. (1); L. L. L. (1); R. Mid. and Basal Zones; R. Lower and Mid. Zones; Rt. Lobar Pneu.	3.8	1.8	336 cc. (100-750)	Five recovered; 1 died.
Li (1932) . . . .	6	8-62	L. U. L. (1); Pleural Effusion; R. M. L. (2); R. L. L. (2); R. Central	6.5	1.8	261 cc. (200-350)	Five recovered; 1 died.
Anderson (1932) . . . .	3	25	L. L. L. (1); R. U. L. (1); R. M. L. and R. L. L. (1)	5	3.0	422 cc. (400-600)	All recovered.
Guadarrama (1932) . . .	1	37	Left side	3	2.0	375 cc. (350-400)	Recovered.
Perleth and Topercer (1932)	7	18-55	L. U. L. (1); R. U. L. (1); R. L. L. (1); Bronchopneumonia; L. L. L. (3)	3.8	1.4	410 cc. (50-500)	Six recovered; 1 died.

and the average amount of air injected at each treatment was 400 cc. for adults. In the entire group, 47 patients recovered and 3 died. All those who have used therapeutic pneumothorax for lobar pneumonia enthusiastically recommend it. They state that following the induction of pneumothorax there is prompt amelioration of the distressing symptoms and there is initiated a series of events almost indistinguishable from spontaneous crisis, with profuse perspiration and fall in temperature in a few hours. Relief of pain is immediate in those cases where pleurisy is present. The improvement is only temporary, however, for on the disappearance of the pulmonary compression all the initial symptoms return. When the compression is maintained for 48 hr. or more the pathologic process usually ends in a definite crisis and normal convalescence follows. In lobar pneumonia, the pleura apparently has an abnormally high absorptive power and to maintain compression for 48 hr. a refill of air is usually necessary in 12 to 18 hr. following the first treatment. In 1 case Coghlan<sup>8</sup> estimated the urinary chlorids and counted the leukocytes before and after the defervescence produced by the artificial pneumothorax. He found a rise of the urinary chlorids of 60% and a fall in the leukocyte count of over 25% less than 24 hr. thereafter.

Despite these almost incredible reports in the literature, we were unwilling to treat patients on this evidence alone, and decided to study the problem in animals. We have therefore conducted a series of experiments on dogs with a comparable, untreated, control group in order to observe in detail the course of lobar pneumonia treated with artificial pneumothorax.

Robertson and his coworkers<sup>14</sup> have shown in their studies on natural immunity that the pneumococcal action of the blood of dogs is not much greater than that of the average human being. While they do not know definitely that this property has the same significance in the immunity of both species, they do have evidence that the pneumococcal power of the blood parallels in general the species resistance to pneumococcus infection.<sup>15,16</sup>

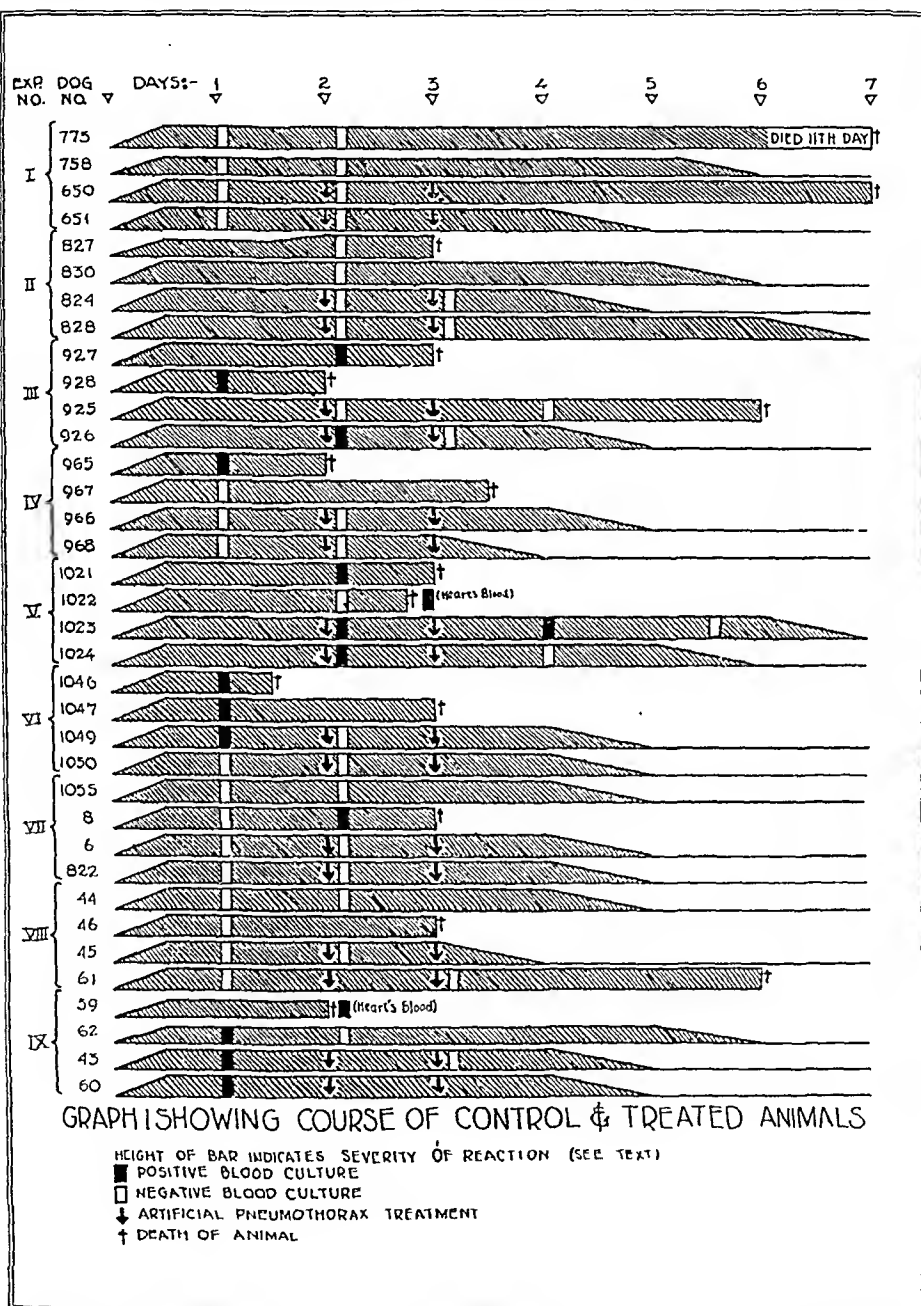
**Method of Production of Lobar Pneumonia in Dogs.** The method employed by us differed in a few details from that used by Robertson and his coworkers.<sup>14</sup> After anesthetization the dogs were bronchoscoped, a No. 8 F. soft rubber catheter was passed through the bronchoscope into the bronchus supplying the lower lobe of the lung desired, and 1 cc. of starch paste containing 0.06 cc. of sedimented, virulent pneumococci was injected through the catheter. Two syringe-barrels-full of air were then injected into the catheter to disperse the starch paste throughout the lobe of the lung supplied by that bronchus. The details of our technique were as follows:

1. *Dogs.* Healthy dogs, either male or female, of average weight of 10 kg. were used.

2. *Pneumococci.* Strains (Types 1 and 3) virulent for mice were used. These organisms were subjected to repeated passage through mice during the course of the study. All cultures used for inoculation were in the phase of active growth.

3. *The Starch-broth mixture* advocated by Robertson and his coworkers<sup>14</sup> was used.

4. *Anesthetization.* In order to obtain anesthesia with just enough relaxation necessary to permit bronchoscopy as well as the requisite fall in temperature for the establishment of pneumonia,<sup>14</sup> a preliminary injection of



morphin sulphate (6 mg. per kg. B.W.) was given. This was followed in 30 min. by the intraperitoneal injection of 15 mg. of sodium amytal per kg. body weight. About 15 min. after the injection of the sodium amytal, bronchoscopic instillation of the culture was made.

5. *Postanesthetic Care.* As the dogs had a subnormal temperature for several hours because of the anesthesia, they were placed on burlap bags in a warm room, lying on the side where the starch paste culture was introduced.

6. *After Care.* The dogs were allowed the liberty of their room and given daily one plentiful supply of cooked scraps and fresh water.

**Experimental.** Thirty-six dogs were used in groups of 4. Two dogs of each group were given pneumothorax and the other 2 were used as controls. Shortly after the injection of morphin there was a drop of between 3° and 4° F. in the temperature. On the day after the inoculation (a) with the starch-paste culture, the temperature was elevated and the dogs were acutely sick. They were usually too ill to walk and ate and drank very little. Physical signs of consolidation could be elicited. Unless treated by pneumothorax, the disease usually progressed and ended fatally on the 2d or 3d day. Of the 36 dogs in our series 14 developed demonstrable blood-stream invasion during life. In 2 additional animals the pneumococcus was recovered in the heart's blood postmortem. Of the 5 dogs which recovered without treatment, 1 had a positive blood culture. He recovered by crisis and was well on the 4th day.

TABLE 2.—DATA OF TREATED DOGS THAT RECOVERED.

Dog No.	Type pneu.	Involvement.	W.B.C. in thousands.	Temperature.	Blood culture.
651	3	R. U. L. R. M. L. R. L. L.	22.4	104.2°	0
824	3	R. L. L. R. M. L.	18.1	104.2°	0
828	3	R. L. L. R. M. L.	16.2	104.6°	0
926	1	R. L. L. R. M. L.	21.2	105.6°	+
966	1	R. L. L. R. M. L.	23.0	104.8°	0
968	1	R. L. L. R. M. L.	22.0	104.2°	0
1023	1	R. U. L. R. U. L. R. M. L. R. L. L.	31.0	105.4°	+*
1024	1	R. U. L. R. M. L. R. L. L.	32.0	105.4°	+
1049	1	L. U. L. L. M. L. L. L. L.	34.0	104.8°	+
1050	1	L. U. L. L. M. L. L. L. L.	32.0	103.2°	0
6	1	L. M. L. L. L. L.	22.0	103.8°	0
822	1	R. L. L. R. M. L.	29.0	103.4°	0
43	1	R. L. L. R. M. L.	34.0	105.4°	+
45	1	R. L. L. R. M. L.	29.0	104.2°	0
60	1	L. L. L. L. M. L.	30.8	105.2°	+

\* Overwhelming blood invasion.



896

FIG. 2.—Dog No. 968. Second day of disease. Lobar pneumonia of all lobes on right side. Left lung normal.



968

FIG. 3.—Dog No. 968. Second day of disease; after artificial pneumothorax 250 c. c. on right side. Slight compression of right lung. Left lung normal.





FIG. 4.—Dog No. 968. Third day of disease. After 250 c. c. of air injected on right side on second day of disease and 300 c. c. on third day. Increase in compression of right lung. Left lung normal.



FIG. 5.—Dog No. 968. Sixth day of disease. Most of pneumothorax absorbed; beginning resolution of the right lung. Left lung normal.

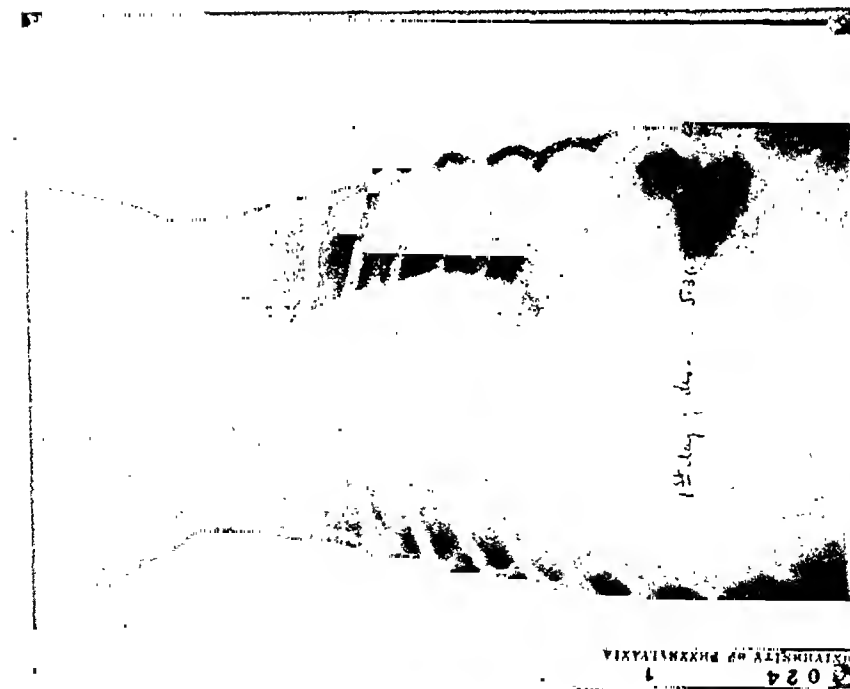


FIG. 7.—Dog No. 1024. Lobar pneumonia involving multiple lobes on right side. Normal aeration of left side.

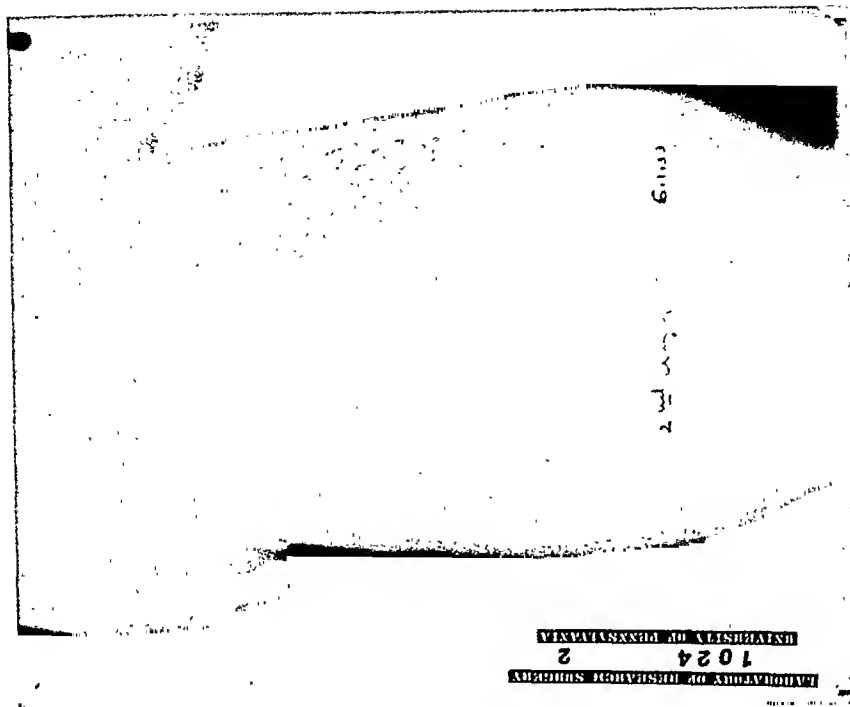


FIG. 8.—Dog No. 1024. Second day of disease. Increased density of right lung. Left side probably normal. Plate underexposed.

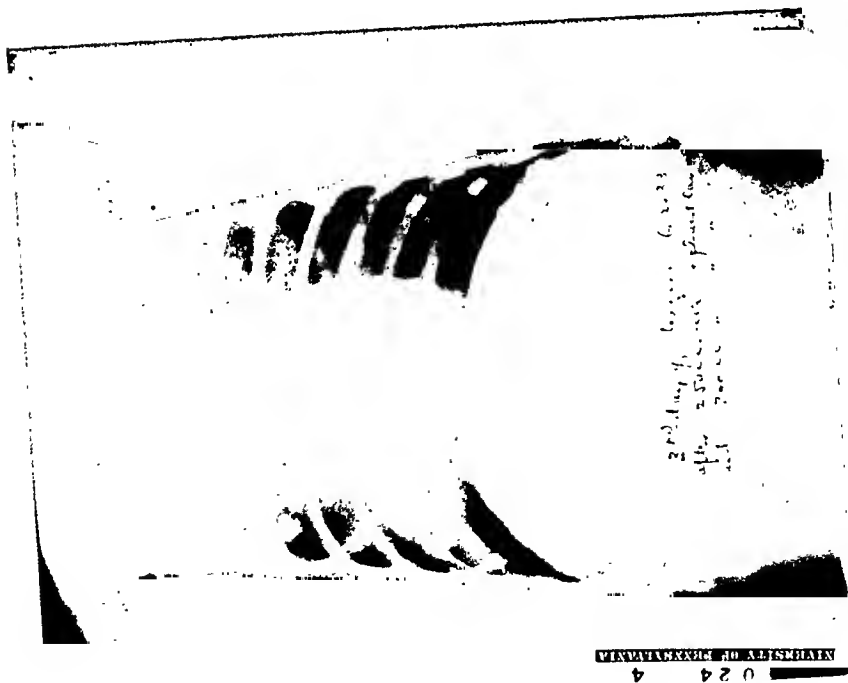


FIG. 9.—Dog No. 1024. Third day of disease, after artificial pneumothorax 250 c. c. on right side on second day and 300 c. c. on third day. Moderate compression of the lobes on right side due to pneumothorax. Left lung normal.



FIG. 10.—Dog No. 1024. Fourth day of disease. Appearance essentially the same as Fig. No. 9. Pneumothorax partially absorbed. Plate overexposed.

(a) For the sake of uniformity and convenience the day following the inoculation of the starch paste culture is called the 1st day of the disease. This differs from the terminology used by Robertson and his coworkers.<sup>14</sup> They showed that the pathologic process begins within a few hours after the inoculation of the starch-paste culture.

The protocols of 7 of the 15 dogs which were treated and recovered follow.

*Dog 968.* After the usual anesthetic (May 16) 1 cc. of starch paste, containing 0.06 cc. of sedimented pneumococci Type 1, was injected into the right lower lobe. On the following day the dog was definitely sick and coughed a good deal. There were physical signs of extensive pulmonary consolidation of all the lobes on the right side. The respirations were deep and fast and there was much drooling from the mouth. On the following day, May 18, the dog was too sick to walk and appeared to be moribund. Artificial pneumothorax (250 cc.) was given on the right side. The following day the dog was running around the room and appeared to be well. A refill of 300 cc. of air was given. The dog made an uneventful recovery. Blood cultures were negative.

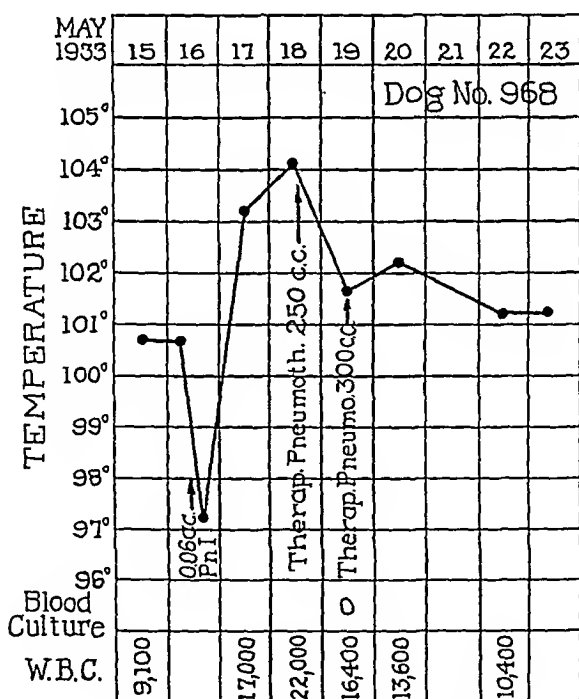


FIG. 1.—Clinical record. Dog No. 968.

*Dog 1024.* After the usual anesthetic (May 30) 1 cc. of starch paste, containing 0.06 cc. sedimented pneumococci Type 1, was injected into the right lower lobe. On the following day the animal was quite sick. The temperature was 105.2° F. and the physical signs were those of consolidation throughout the right chest. On the following day the dog was still very sick. The temperature and physical findings were unchanged. The blood culture on this day was positive. Artificial pneumothorax (250 cc.) was given on the right side. On the following day (June 2) the dog was much

better, breathing more easily and running around the room. The temperature and leukocyte count were lower. A refill of 300 cc. air was given. The dog made an uneventful recovery and appeared to be perfectly well on the following day.

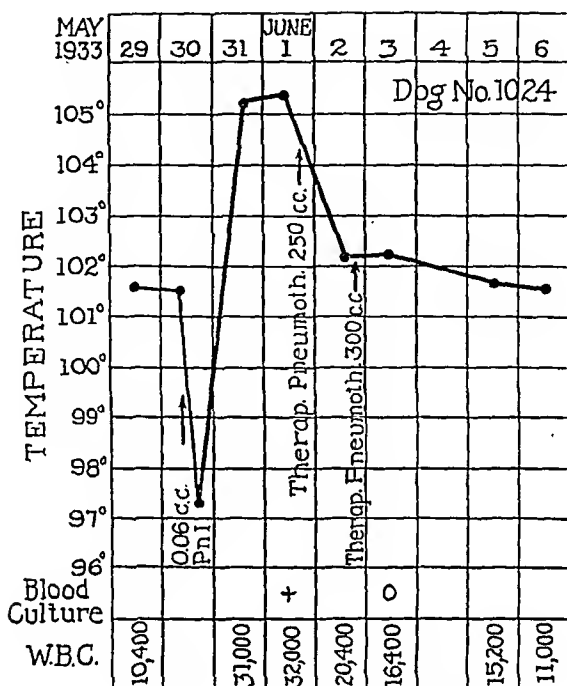


FIG. 6.—Clinical record. Dog No. 1024.

*Dog 1023.* After the usual anesthetic (May 30) 1 cc. of starch paste, containing 0.06 cc. of sedimented pneumococci Type 1, was injected into the right lower lobe. On the following day the dog was definitely ill. The temperature was 104.8° F. On June 1 the dog was very sick, breathing rapidly and deeply. The temperature was 105.2° F. Blood culture taken on this day showed tremendous blood invasion (Fig. 11). Artificial pneumothorax (250 cc.) was given on the right side. On the following day the dog was still quite sick although the temperature and leukocyte count were lower. The blood culture on this day showed 5 colonies to 2 cc. of blood. A refill of 300 cc. of air was given. On June 3, the dog was better although the temperature was somewhat higher than at the time of the second treatment. From this point on, the temperature subsided and the dog made an uneventful recovery. The rise in temperature following the second treatment may have been due to the persistence of blood-stream invasion.

The interesting feature of this case was the fact that recovery followed pneumothorax treatment despite tremendous blood-stream invasion. On the day following treatment, the dog appeared to be much better and ran around the room. The temperature was, however, still elevated. This can, no doubt, be explained by the fact that the animal still had a positive blood culture of 5 colonies to 2 cc. of blood.

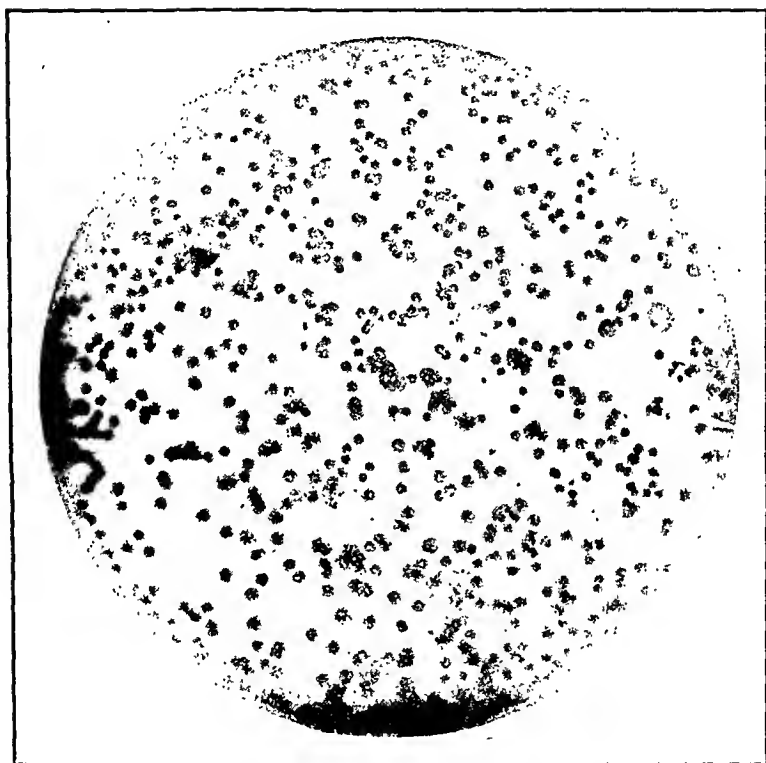


FIG. 11.—Dog 1023. Colonies from blood culture (2 cc.) on 2d day of disease (before artificial pneumothorax).



*Dog 60.* After the usual anesthetic (August 22) 1 cc. of starch paste, containing 0.06 cc. of sedimented pneumococci Type 1, was injected into the left lower lobe. On the following day the dog was very sick and drooled at the mouth. There were physical signs of extensive consolidation on the left side. The blood culture was positive. On August 24 the animal appeared moribund. Artificial pneumothorax (300 cc.) was given on the left side. On the following day the dog was much better. The temperature was normal and the blood culture negative. On that day a refill of 250 cc. of air was given and the dog made an uneventful recovery.

*Dog 1049.* After the usual anesthetic (June 20) 1 cc. of starch paste, containing 0.06 cc. sedimented pneumococci Type 1, was injected into the left lower lobe. On the following day the dog was very sick; respirations were rapid and deep, temperature was 105° F. Blood culture taken on this day was positive. On June 22 the dog appeared moribund. Artificial

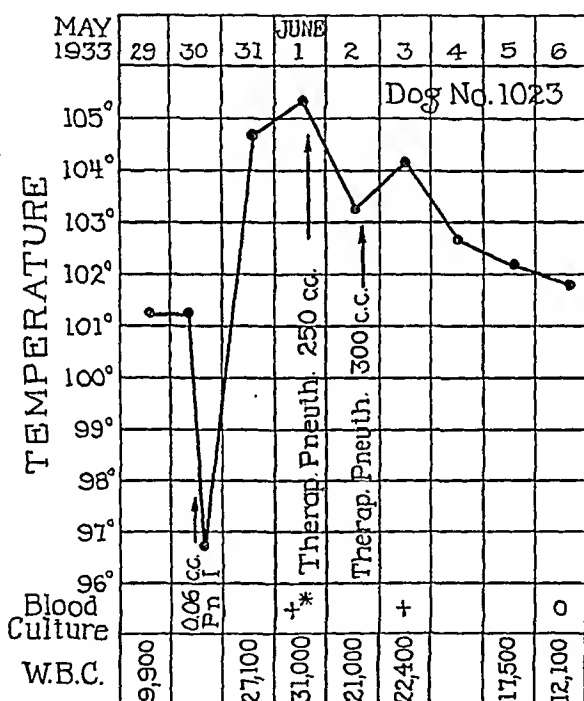


FIG. 12.—Clinical record. Dog No. 1023.

pneumothorax (250 cc.) was given on the left side. The following day the dog was much better and a refill of 300 cc. of air was given. The blood culture taken this day showed no growth. The dog made an uneventful recovery.

*Dog 43.* After the usual anesthetic (August 22) 1 cc. of starch paste, containing 0.06 cc. of sedimented pneumococci Type 1, was injected into the right lower lobe. On the following day the dog was very sick. Respirations were rapid and deep; temperature was 105.2° F. The blood culture taken on this day was positive. On August 24 the animal was worse, panting rapidly and drooling from the mouth. Artificial pneumothorax (300 cc.) was given in the right side. On the following day the animal was much better and ran around the room. The blood culture taken on this day was negative. A refill of 250 cc. of air was given and the dog made an uneventful recovery.



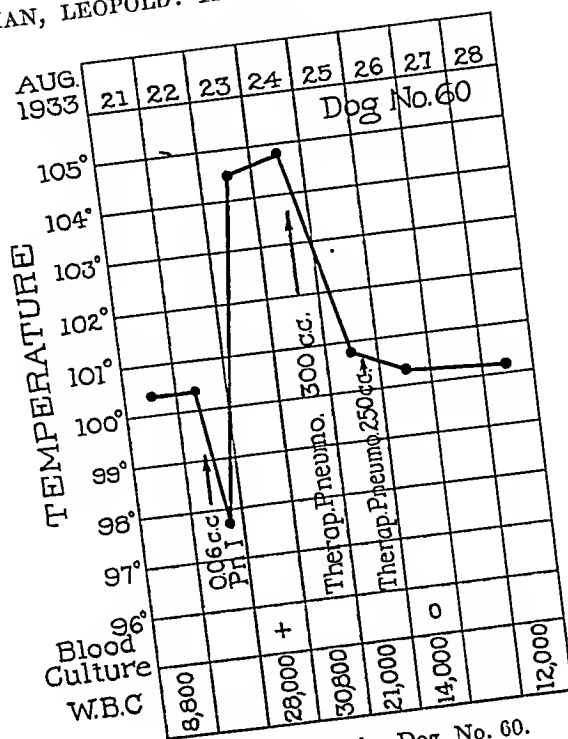


Fig. 17.—Clinical record. Dog No. 60.

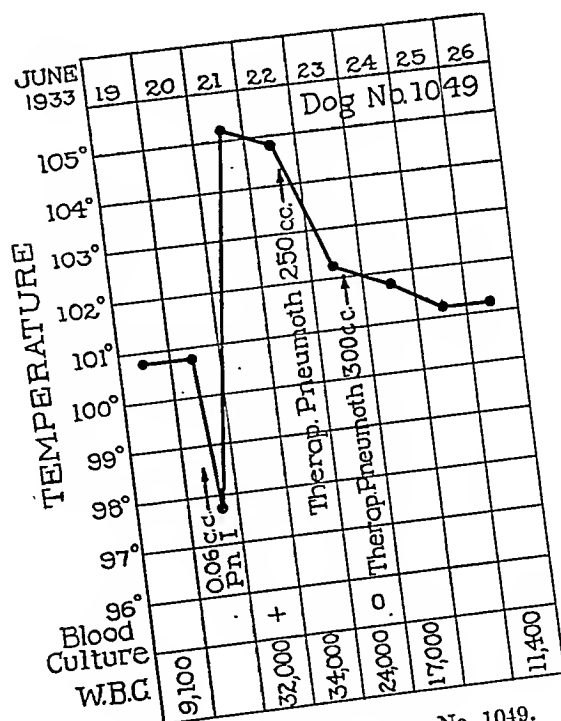


Fig. 22.—Clinical record. Dog No. 1049.

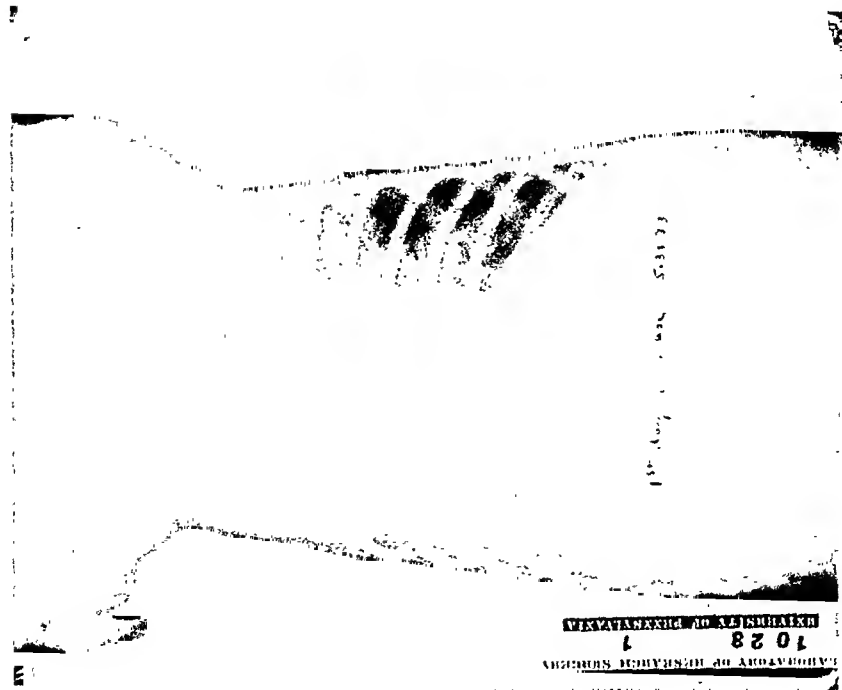


FIG. 13.—Dog No. 1023. Lobar pneumonia involving all lobes on right side. Left lung aerating normally. Heart displaced to affected side.

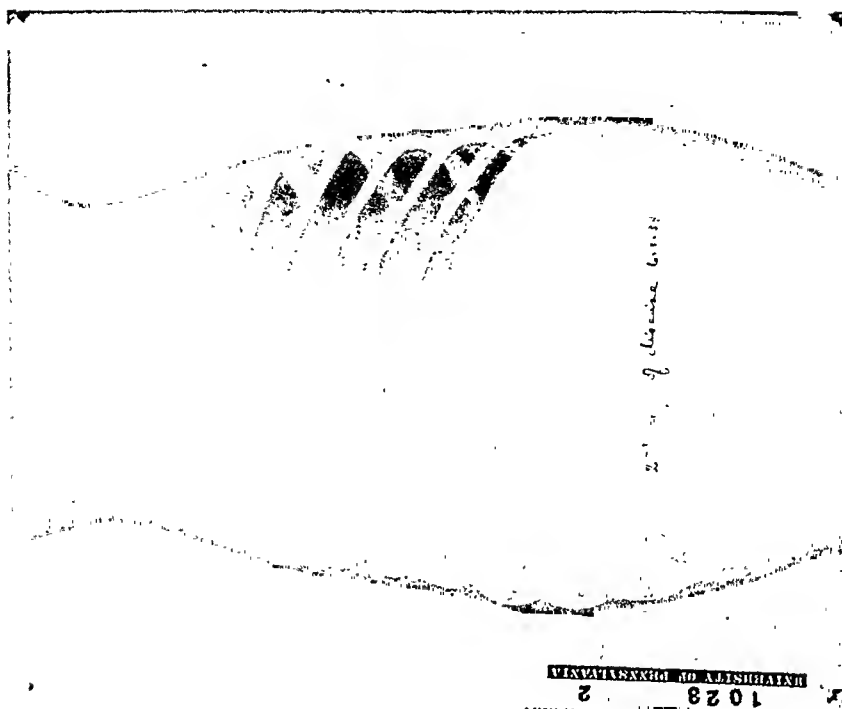


FIG. 14.—Dog No. 1023. Involvement of right lung by lobar pneumonia is shown to better advantage. Heart displaced to affected side. Left lung aerating normally.



FIG. 15.—Dog No. 1023. Fourth day of disease after artificial pneumothorax 250 c. c. on second day and 300 c. c. on third day of disease. Moderate compression of lobes on right side. Normal aeration of left side.

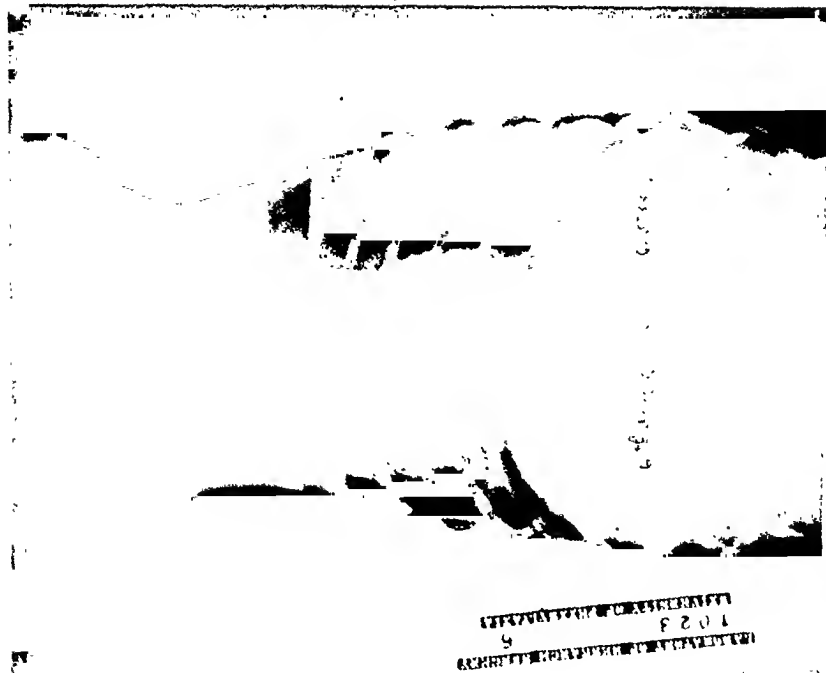


FIG. 16.—Dog No. 1023. Sixth day of disease. The pneumothorax is largely absorbed. Considerable resolution has taken place.



FIG. 18.—Dog No. 60. First day of disease. Increased density of all lobes on left side. Right lung aerating normally.

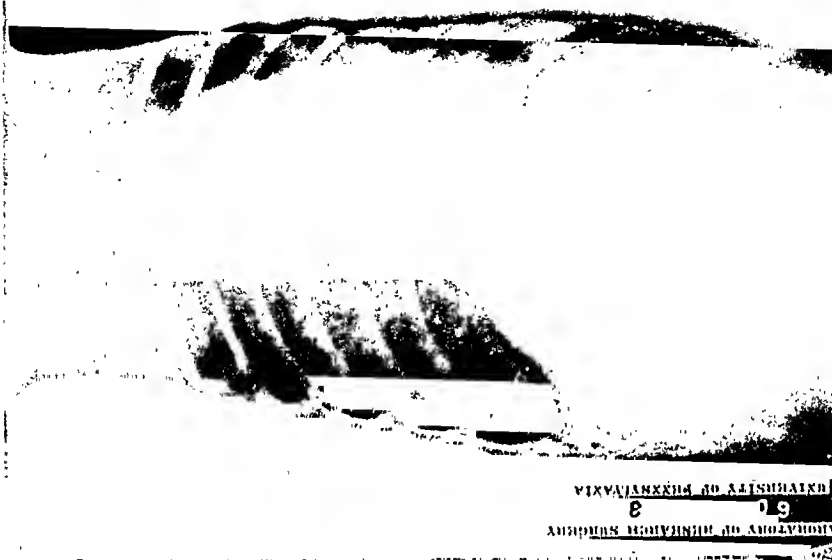


FIG. 19.—Dog No. 60. Second day of disease; after artificial pneumothorax 250 c. c. left side. Moderate compression of left lung due to pneumothorax.

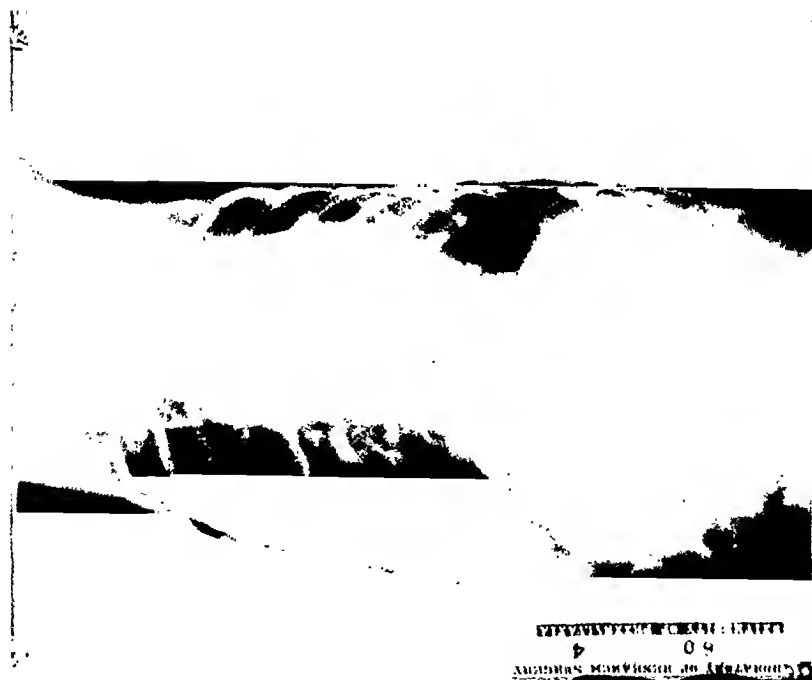


FIG. 20.—Dog No. 60. Third day of disease after artificial pneumothorax 250 c. c. on second day of disease and 300 c. c. on third day. Considerable compression of left lung due to artificial pneumothorax. Right lung aerating normally.

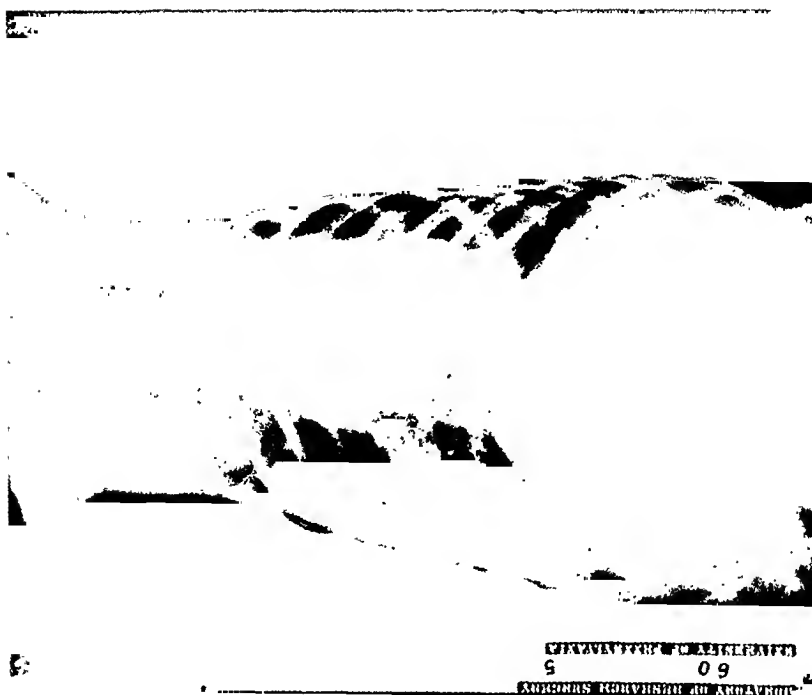


FIG. 21.—Dog No. 60. Fourth day of disease. Beginning re-expansion of left lung with beginning resolution. Right lung aerating normally.



FIG. 23.—Dog No. 1049. Second day of disease. Lobar pneumonia involving two of the lobes and possibly the third on left side. Right lung aerating normally.



FIG. 24.—Dog No. 1049. Second day of disease after artificial pneumothorax 250 c. c. (left). Moderate compression of lobes on left due to pneumothorax. Right lung aerating normally.

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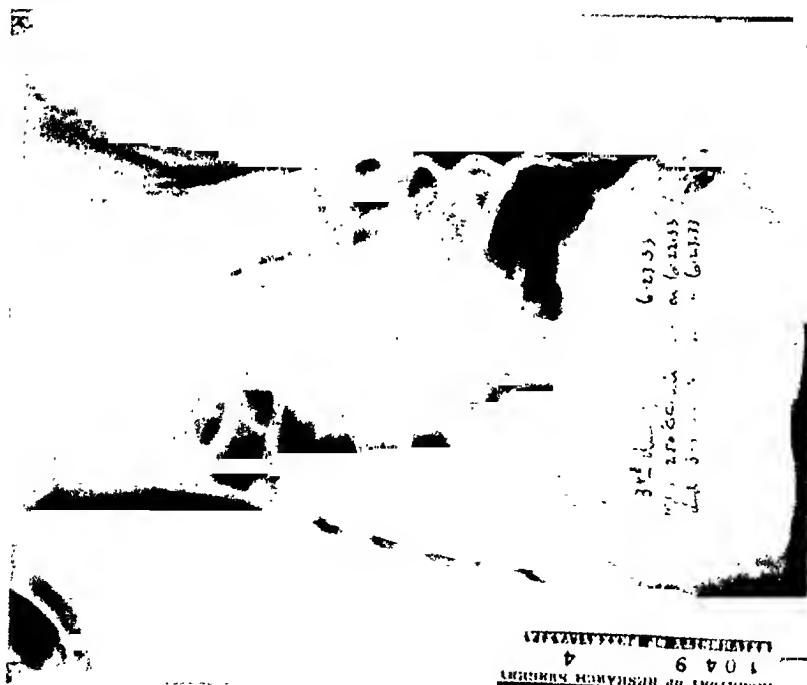


Fig. 25.—Dog No. 1049. Third day of disease after 250 c. c. air on second day of disease and 300 c. c. on third day. Moderate compression left lung with beginning clearing of left lower lobe.

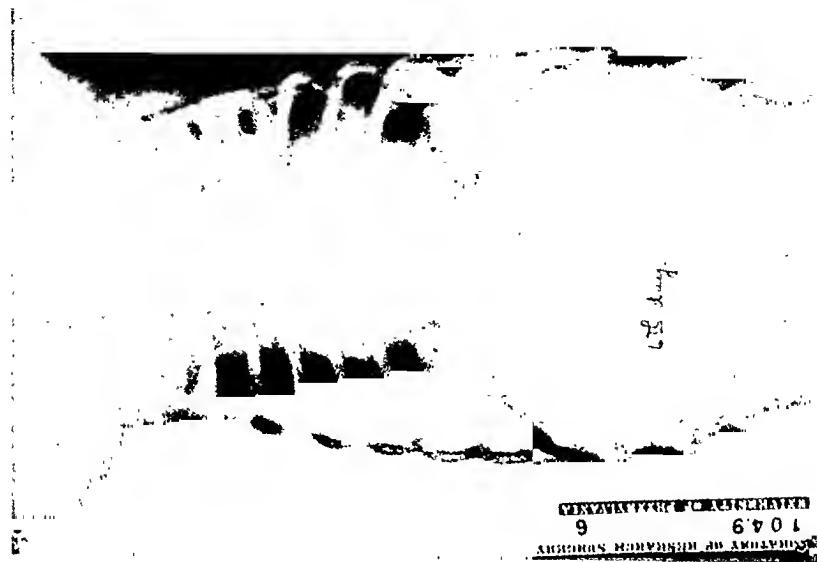


Fig. 26.—Dog No. 1049. Sixth day of disease. The pneumothorax has largely disappeared and there has been a considerable amount of resolution. Right lung normal.

22

LABORATORY OF INVESTIGATION  
43  
2



FIG. 28.—Dog No. 43. First day of disease; lobar pneumonia involving the upper and lower lobes and partial involvement of mid-lobe on right side. Left lung normal.

22

LABORATORY OF INVESTIGATION  
43  
2



FIG. 29.—Dog No. 43. Second day of disease, after artificial pneumothorax 250 c. c. on right side. Moderate compression of right lung.



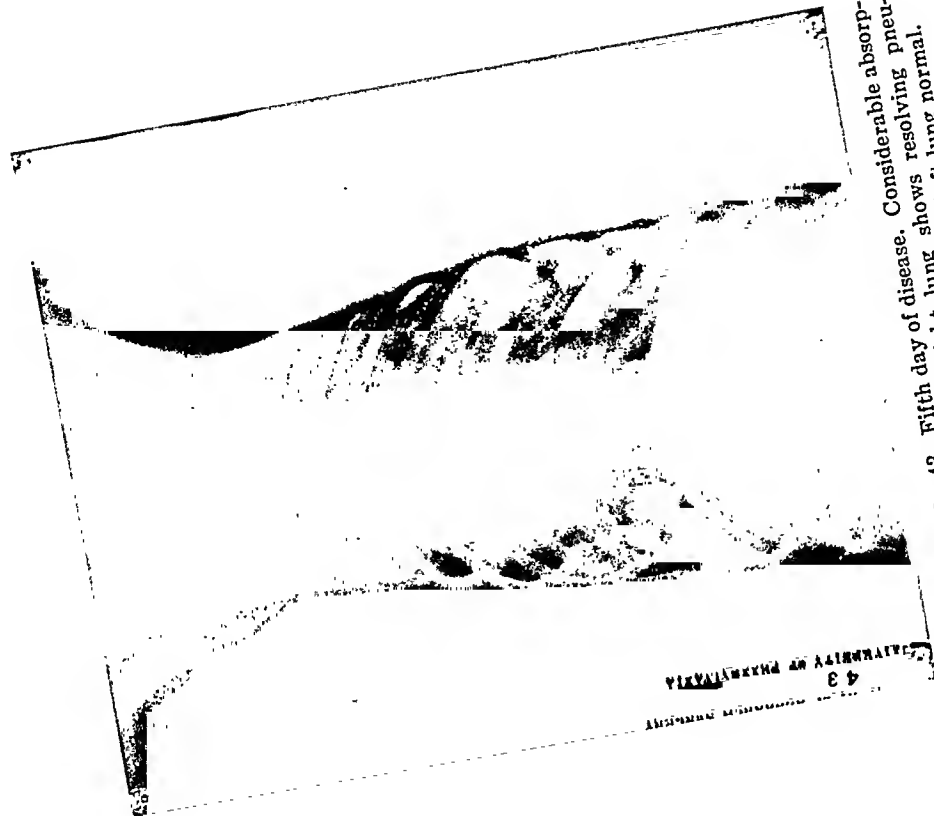


FIG. 31.—Dog No. 43. Fifth day of disease. Considerable absorption of the pneumothorax. Right lung shows resolving pneumonia. Heart still toward affected side.



FIG. 30.—Dog No. 43. Third day of disease after 250 c. c. air on second day and 300 c. c. on third day of disease. Increased compression right side. Heart toward affected side.

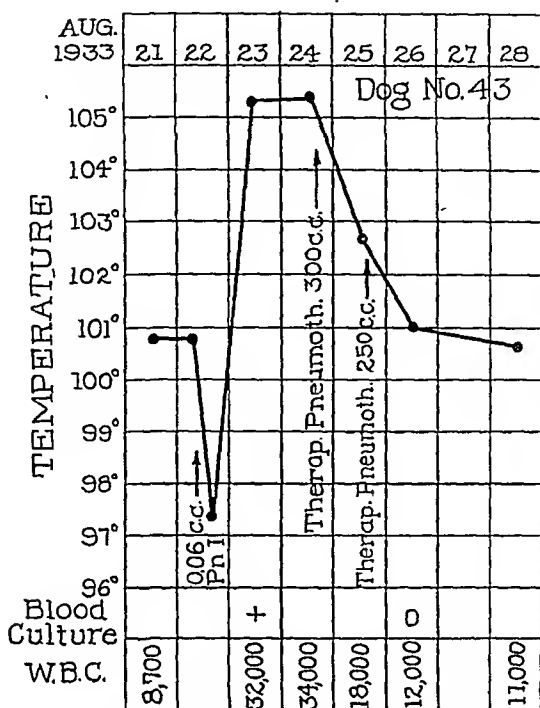


FIG. 27.—Clinical record. Dog No. 43.

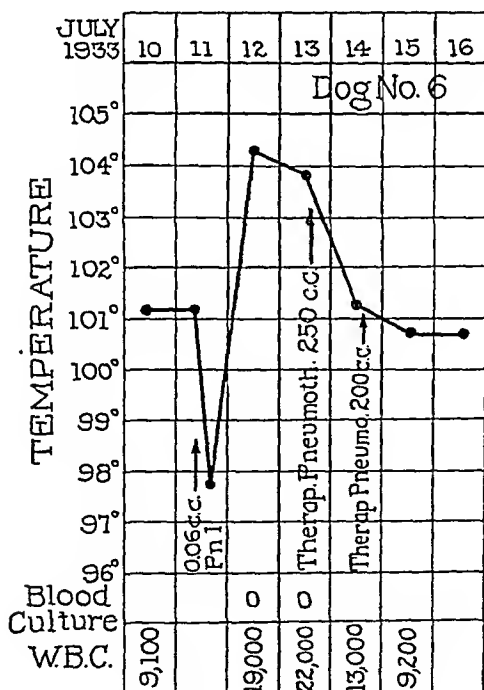


FIG. 32.—Clinical record. Dog No. 6.

*Dog 6.* After the usual anesthetic (July 11) 1 cc. of starch paste, containing 0.06 cc. of sedimented pneumococci Type 1, was injected into the left lower lobe. On the following day the animal was definitely sick. The temperature was 104.2° F. The blood culture taken on this day showed no growth. On July 13 the dog appeared more acutely ill and breathed rapidly and deeply. Artificial pneumothorax of 250 cc. was given on the left side. On the following day the dog was much better, ate well and ran around the room. A refill of 200 cc. of air was given on this day. The dog made an uneventful recovery.

In our series of 36 dogs, 18 were treated with artificial pneumothorax on the 2d day of the disease with 15 recoveries and 3 deaths. The 2d day was chosen as the disease produced in this way was thought to have reached its height at about that time.

On the day following the initial injection of air there was, with two exceptions (Dogs 650 and 925) marked improvement in the condition of the animals. A further refill was given on the day following the initial injection. No subsequent injections were given and no other form of therapy was used at any time.

The pulmonary compression resulting from the introduction of 250 or 300 cc. of air produced in the animals a condition analogous to the crisis seen in lobar pneumonia in man. There was an abrupt drop of temperature and leukocyte count, with easier and more normal respirations and an appearance of wellbeing. The dogs promptly recovered sufficiently to walk and take food. The blood cultures in those dogs in which there was blood invasion before the institution of artificial pneumothorax were usually negative on the day after the treatment, and in the 1 case (Dog 1023) where the blood stream invasion was extraordinarily severe it was found to be reduced to 5 colonies per 2 cc. of blood on the day after the second treatment.

An analysis of the 3 deaths which occurred in those animals which were treated with artificial pneumothorax follows:

TABLE 3.—DATA OF DOGS DYING AFTER TREATMENT.

Dog No.	Type pneu.	Involv.	W.B.C. in thousands.	Temp.	Blood culture.	Remarks.
650	3	R. L. L. R. M. L.	23.4	104.2°	0	150 cc. air 2d day. 150 cc. air 3d day. Died 6th day.
925	1	R. U. L. R. M. L. R. L. L.	26.0	104.8°	0	Died 5th day. Lung abscess and sanguiniferous pleurisy.
61	1	R. L. L. R. M. L.	30.0	105.2°	0	Died 5th day. Hemor. enteritis.

*Dog 650.* After the usual anesthetic (March 15), 0.06 cc. sedimented pneumococci Type 1 in 1 cc. of starch paste was injected into the right lower lobe. On the following day the temperature was elevated to 104.6° F. and

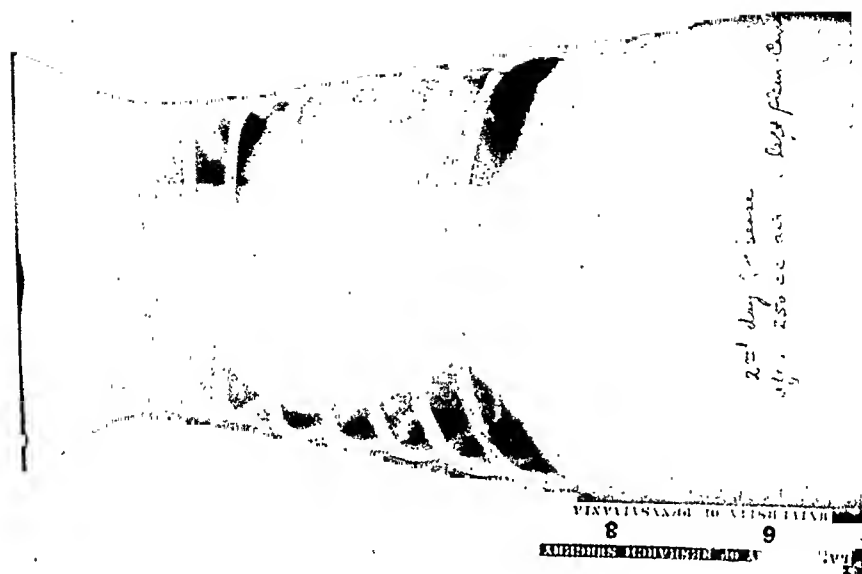


FIG. 33.—Dog No. 6. First day of disease; lobar pneumonia involving the lobes on left side. Heart toward the affected side. Normal aeration of right side.

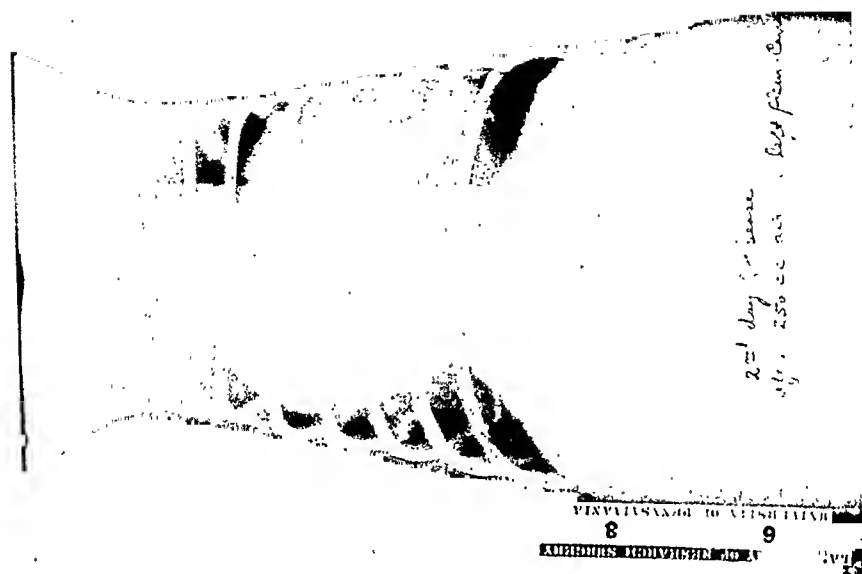


FIG. 34.—Dog No. 6. Second day of disease, after artificial pneumothorax 250 c. c. Considerable compression of lobes on left. Heart displaced away from affected side. Normal aeration of right lung.

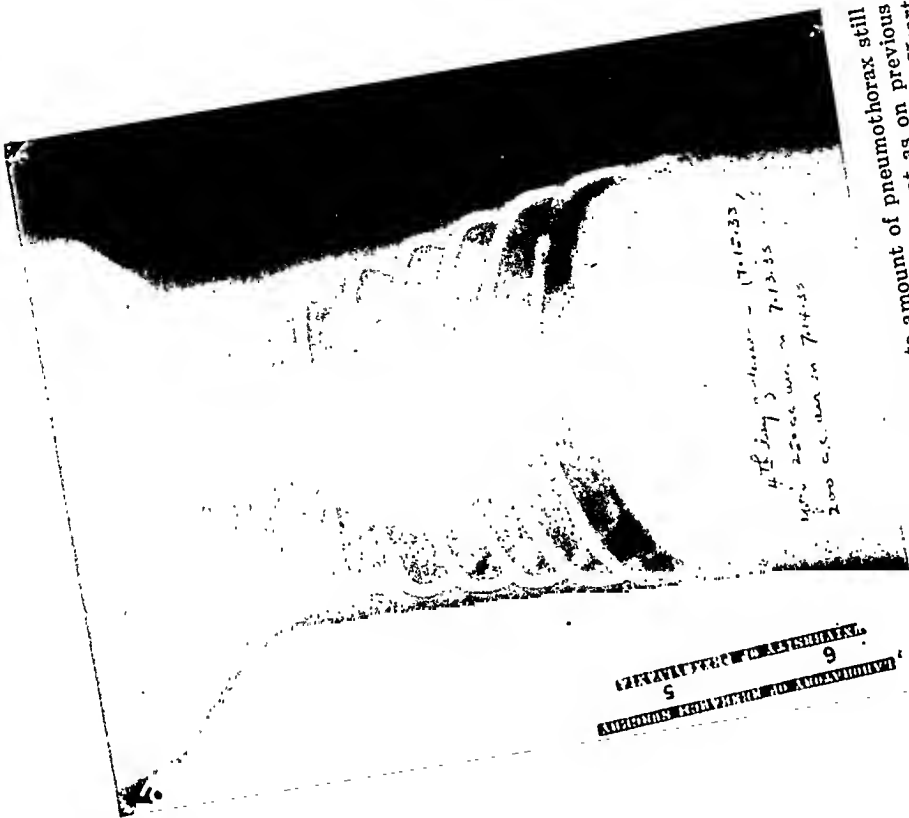


FIG. 36.—Dog No. 6. Moderate amount of pneumothorax still present. Density of diseased lung not as great as on previous examination suggesting that there is beginning resolution. Heart slightly to the right.

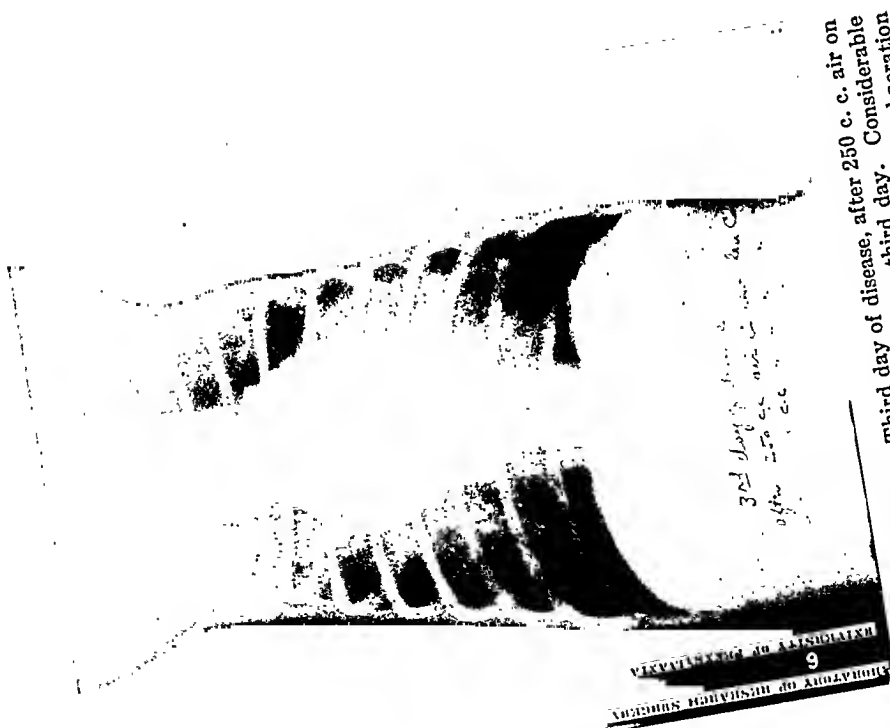


FIG. 35.—Dog No. 6. Third day of disease, after 250 c. c. air on second day of disease and 300 c. c. on third day. Considerable compression of lobes on left. Heart in mid-line. Normal aeration of right lung.

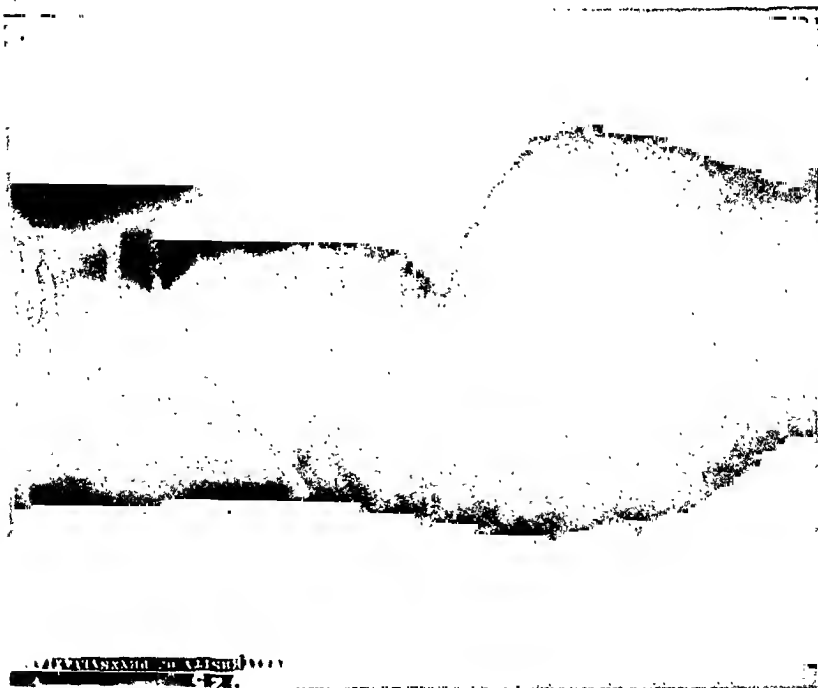


Fig. 37.—Dog No. 925. Second day of disease. Beginning consolidation of all lobes on right side. Heart in normal position.

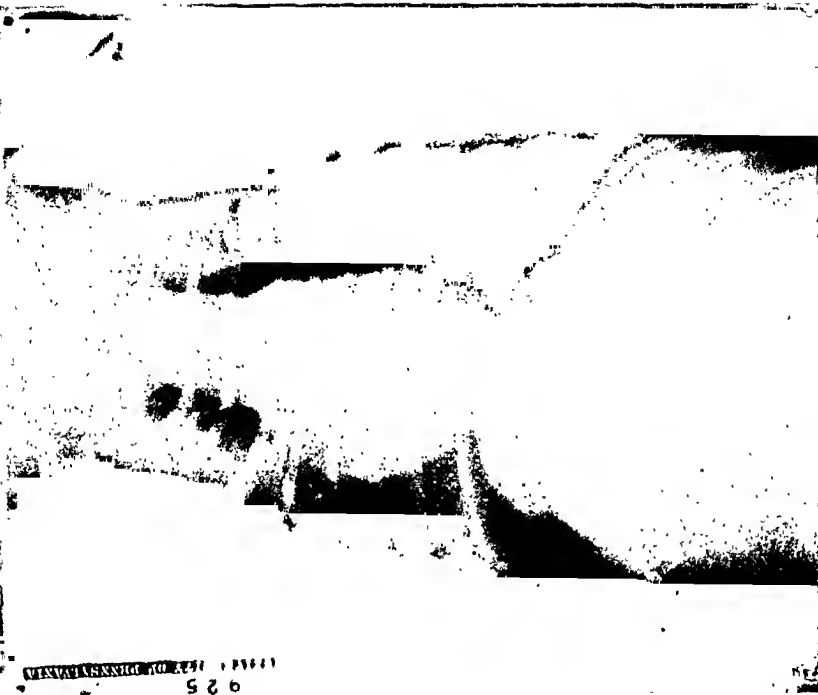


Fig. 38.—Dog No. 925. Second day of disease after injection of 275 c. c. of air on right side. Moderate pneumothorax present.



FIG. 39.—Dog No. 925. Third day of disease after 275 c. c. of air on second day and 250 c. c. of air on third day. Consolidation of all lobes on the right side and moderate pneumothorax. Small circular cavity (abscess) in right lower lobe.

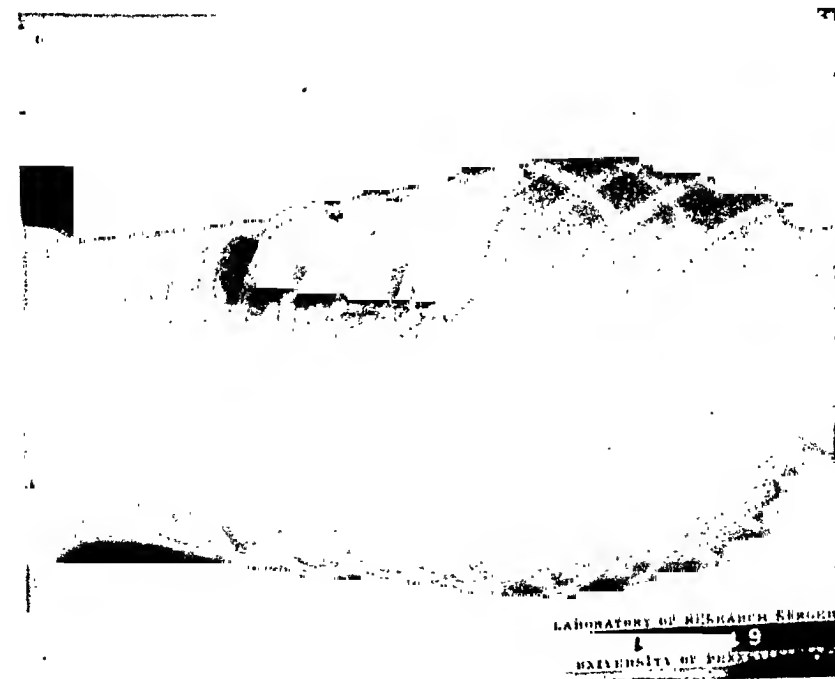


FIG. 40.—Dog No. 61. First day of disease. Complete consolidation of all lobes on right side. Heart toward affected side.

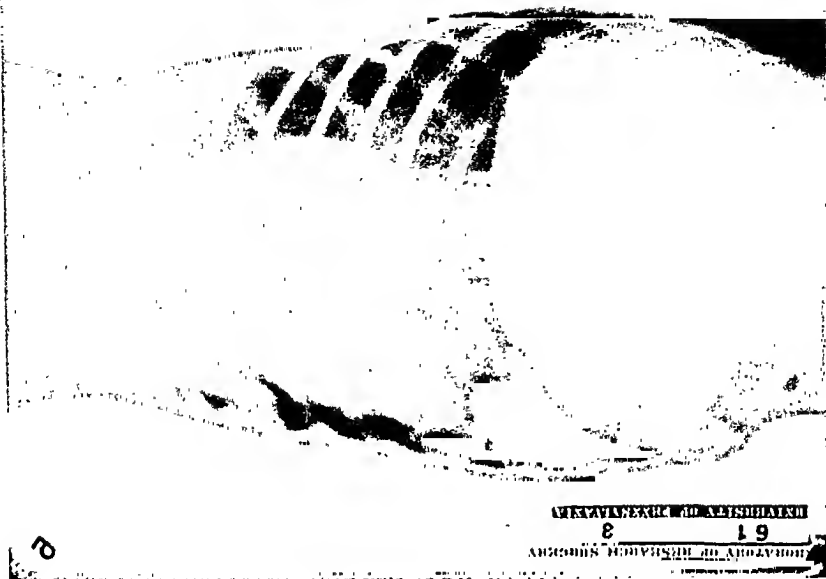


FIG. 41.—Dog No. 61. Third day of disease after 300 c. c. air on right side on second day and 250 c. c. on third day. Compression of all lobes on right side by pneumothorax. Heart in normal position.



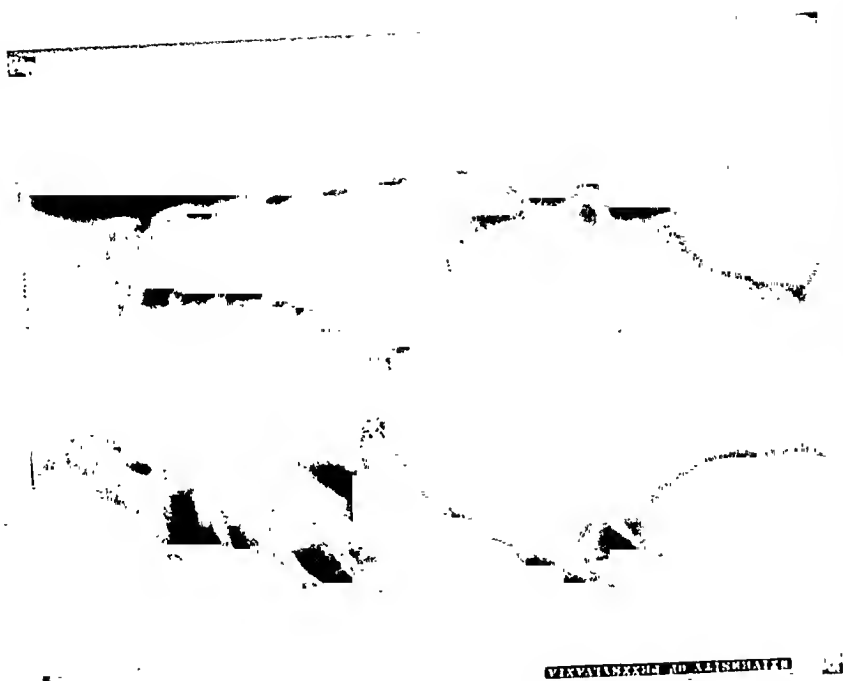


FIG. 42.—Dog No. 61. Fourth day of disease. Resolving pneumonia of all lobes on the right side. Some pneumothorax still present. Heart in normal position.

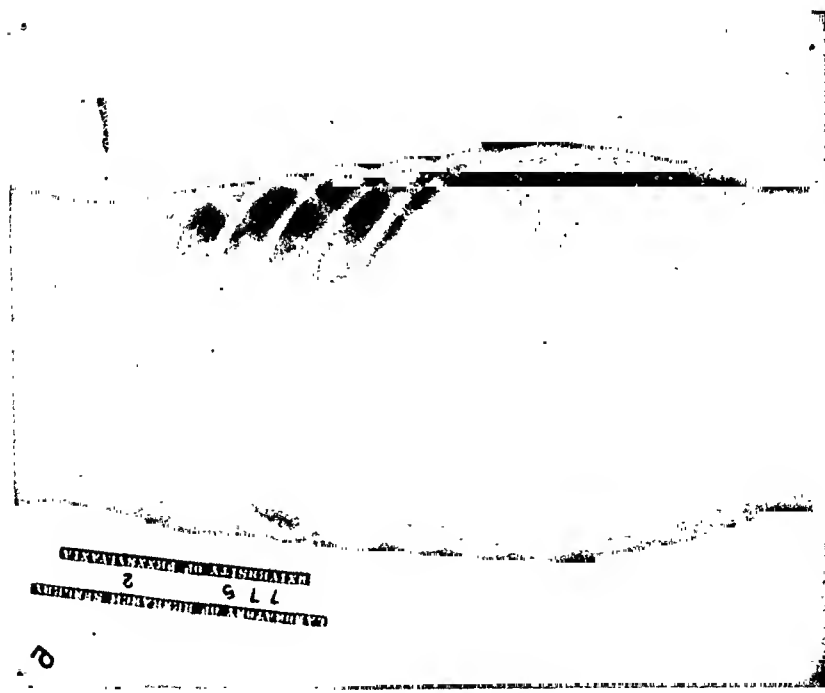


FIG. 43.—Dog No. 775. Fourth day of disease. Consolidation of all lobes on right side.

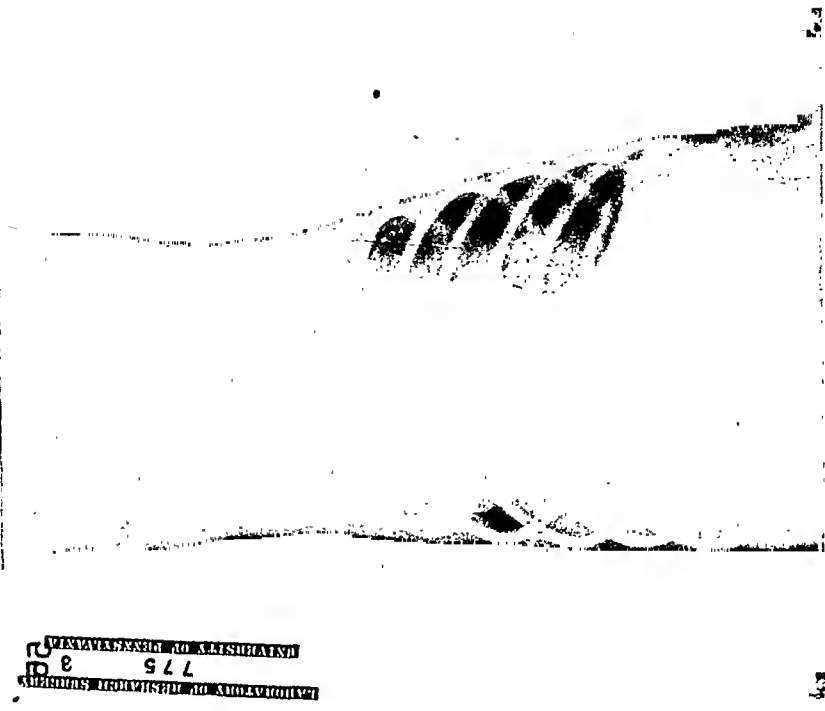


FIG. 44.—Dog No. 775. Fifth day of disease. Dense consolidation of upper and lower lobes. Slight clearing of mid zone. Death occurred on the eleventh day.



FIG. 45.—Dog No. 827. First day of disease. No evidence of consolidation.

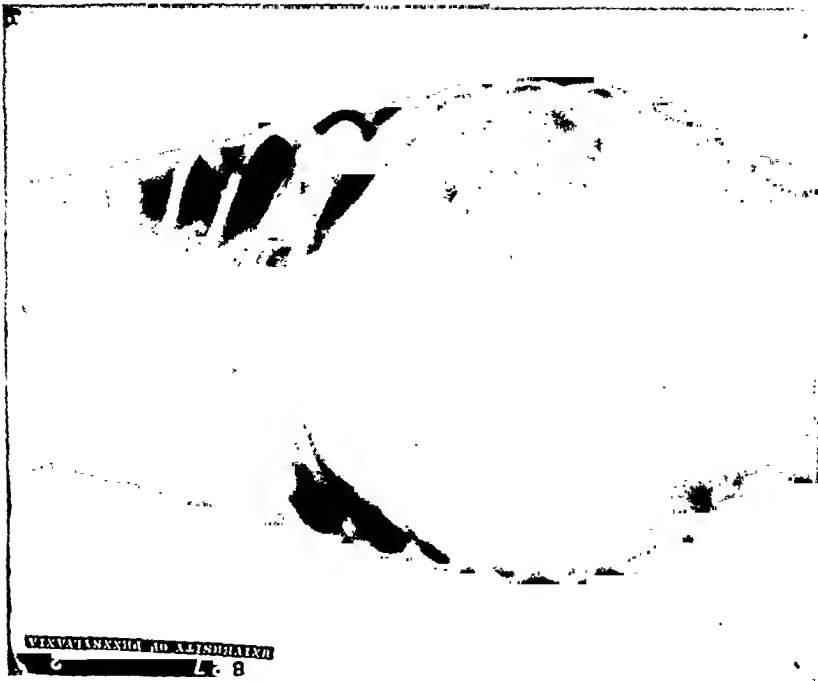


FIG. 46.—Dog No. 827. Second day. Complete consolidation of right upper lobe and right middle lobe. Heart drawn slightly to affected side. Death occurred on third day.

the leukocyte count was 24,000. The blood culture was negative. On March 17 the dog looked very sick. The temperature was 104.2° F. Artificial pneumothorax (150 cc.) was given on the right side. On the following day the animal appeared improved. The temperature was 103.4° F. and the leukocyte count 21,000. A refill of 150 cc. of air was given. On March 19 the dog was more active and breathed easier. The leukocytes numbered 11,400 and temperature was 104.2° F. Two days later the dog appeared to be worse and died the following day.

*Postmortem examination* revealed gray hepatization of the right middle and lower lobes. There was no fluid in the pleural cavities. The left lung appeared normal. This dog died of uncomplicated pneumonia. The temperature was not materially influenced by either the first or second treatment. The amount of air introduced at each of our instillations, in the light of our subsequent experience, may have been insufficient to produce the characteristic response.

*Dog 925.* After the usual anesthetic (May 9) 1 cc. of starch paste, containing 0.06 cc. of sedimented pneumococci Type 1, was injected into the right lower lobe. On the following day the animal was very sick; the temperature was 104.8° F. and the leukocyte count 16,000. Artificial pneumothorax (275 cc.) was given on the right side. On May 13 the dog appeared to be just as sick as before the treatment was given. The temperature was 104.2° F., leukocyte count 22,000. The dog coughed a good deal and expectorated a thick mucoid material. A refill of 250 cc. of air was given. The animal became steadily worse and died on May 15.

*Postmortem examination* revealed both pleural cavities filled with bloody fluid. Cultures made from this showed a mixed growth of organisms with pneumococci predominating. The entire right lung was in a state of gray hepatization. The left lung, except that it was water-logged (soaked in the pleural fluid) looked normal. In the right lower lobe there was a dark indentation of the lung with surrounding softening of the lung tissue. This proved to be an abscess and its location corresponded with the interspace where the initial needle puncture was made in giving the artificial pneumothorax.

This dog did not react as did the others to the artificial pneumothorax. We think it is fair to surmise that at the time of the initial injection of air the needle, as the result of improper technique, penetrated the lung with resulting abscess and empyema.

*Dog 61.* After the usual anesthetic (August 22) 1 cc. of starch paste, containing 0.06 cc. sedimented pneumococci Type 1, was injected into the right lower lobe. On the following day the animal was very sick; temperature 105.4° F., leukocyte count 31,000. On August 24 the dog was still sicker. Artificial pneumothorax (300 cc.) was given on the right side. The following day the animal was much better; the temperature was 102.4° F., leukocytes 22,000. A refill of 250 cc. of air was given. At this time the dog had some abdominal distention and a bloody diarrhea. A roentgenogram showed good compression on the right side. The bloody diarrhea and abdominal distention persisted and the dog died on the following day.

In view of the satisfactory response to treatment, confirmed roentgenographically (Figs. 40, 41 and 42), we believe, in view of the hemorrhagic enteritis, that this dog died of an unrelated intercurrent infection. We regret the fact that this animal was the only one in the entire series which was not examined postmortem.

Of the 18 untreated dogs used as controls, 13 died and 5 recovered.

At postmortem each of the 13 animals showed unilateral consolidation. These dogs died, for the most part, on the 2d or 3d day of the disease. At the time of death the lesion had always extended to more than one lobe and usually involved the entire lung, which was in the stage of grayish-red hepatization. A variable amount of fibrinous pleurisy was present over the consolidated lung. The pleuræ contained no fluid.

TABLE 4.—DATA OF UNTREATED DOGS THAT DIED.

Dog No.	Type pneu.	Involv.	W.B.C. in thous-ands.	Temp.	Blood culture.	Remarks.
775	3	R. U. L. R. M. L. R. L. L.	26.0	102.8°	0	Died 11th day.
827	3	R. U. L. R. M. L.	14.4	103.8°	0	Died 3d day.
927	1	R. M. L. R. L. L.	17.8	103.2°	+	Died 2d day.
928	1	R. L. L. R. M. L.	18.1	101.8°	+	Died 2d day.
965	1	R. U. L. R. M. L. R. L. L.	18.8	104.2°	+	Died 2d day.
967	1	R. L. L. Part of R. M. L.	23.0	104.2°	0	Died 3d day.
1021	1	R. U. L. R. M. L. R. L. L.	27.0	104.2°	+	Died approx. 60 hr. after inoculation.
1022	1	R. U. L. R. M. L. R. L. L.	30.0	104.8°	..	Died approx. 36 hr. after inoculation.
1046	1	L. U. L. L. M. L. L. L. L.	25.0	104.2°	+	Heart blood +. Died approx. 36 hr. after inoculation.
1047	1	L. U. L. L. M. L. L. L. L.	26.4	104.4°	+	Died 3d day.
8	1	L. U. L. L. M. L. L. L. L.	22.0	103.4°	+	Died 3d day.
46	1	R. L. L. R. M. L.	31.0	102.4°	0	Died approx. 60 hr. after inoculation.
59	1	L. L. L. L. M. L.	....	.....	..	Died approx. 24 hr. after inoculation. Heart blood +.

Of the 5 dogs which recovered without treatment only 1 had a positive blood culture. These dogs recovered by crisis on the 4th or 5th day of the disease.

*Changes of Position of Thoracic Viscera During Experimental Pneumonia.* Some of our dogs, by roentgenogram, before introduction of air, showed cardiac and mediastinal displacement toward the affected side and elevation of the diaphragm on the same side. This was observed also by Robertson and his coworkers.<sup>14</sup> They

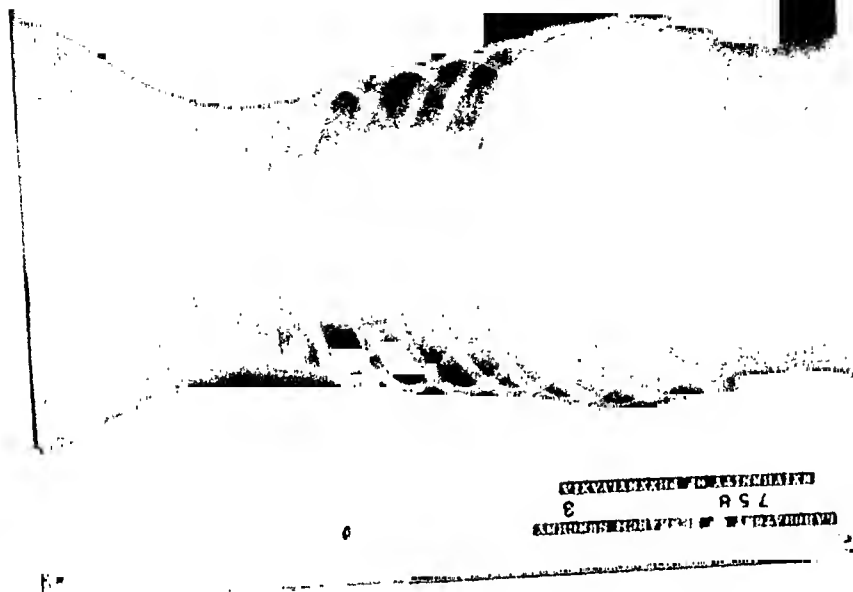


FIG. 48.—Dog No. 758. Third day of disease. Spontaneous resolution of all lobes on right side. Heart in normal position. Uneventful recovery.

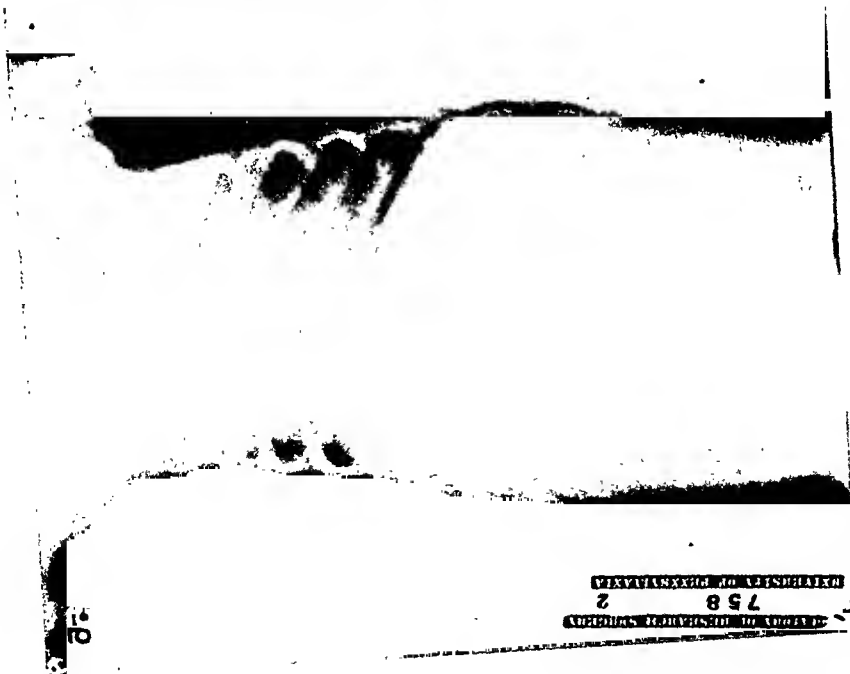


FIG. 47.—Dog No. 758. Second day of disease. Beginning consolidation of all lobes on right side. Heart toward affected side.

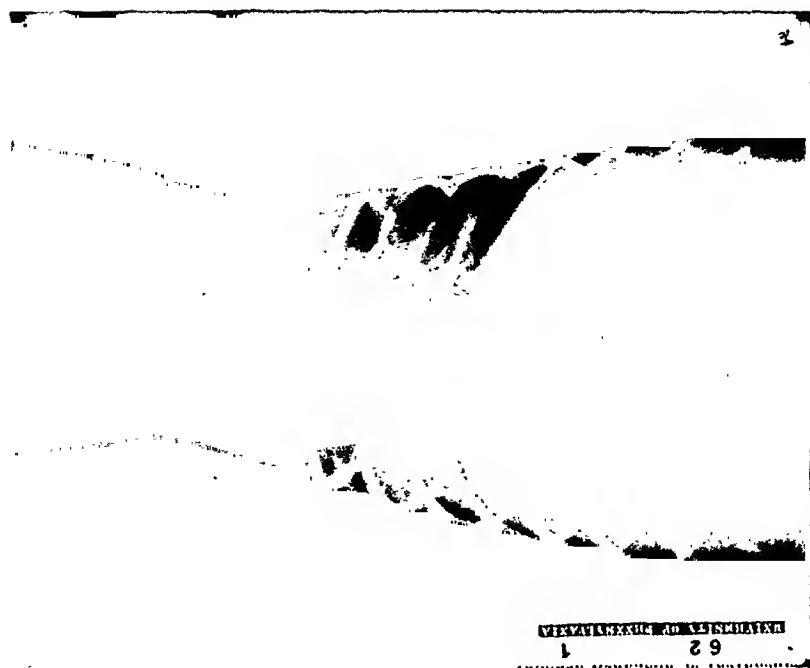


FIG. 49.—Dog No. 62. First day of disease. Consolidation of all lobes on right side. Heart toward affected side.

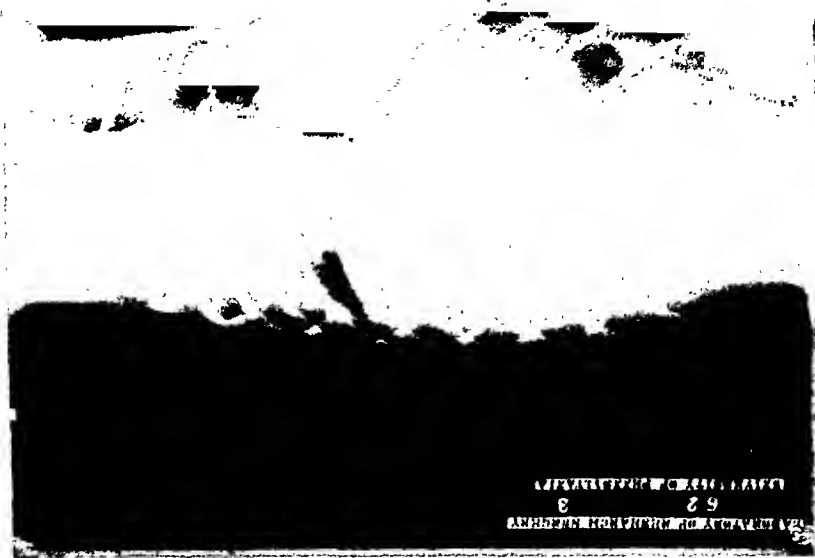


FIG. 50.—Dog No. 62. Third day of disease. Beginning spontaneous resolution in right lower lobe. Heart still toward affected side. Positive blood culture. Uneventful recovery.

found that when the disease process spread rapidly, such as that which occurred after large doses of the pneumococci were injected, the heart shadow showed an early and marked displacement toward the affected side. Even with densely consolidated lung this displacement was observed. Wu,<sup>18</sup> in a study of visceral displacement

TABLE 5.—DATA OF UNTREATED DOGS THAT RECOVERED.

Dog No.	Type pneu.	Involv.	W.B.C. in thousands.	Temp.	Blood culture.
758	3	R. U. L. R. M. L. R. L. L.	23.0	102.6°	0
830	3	L. U. L. L. M. L. L. L. L.	15.4	104.6°	0
1055	1	R. L. L.	26.0	102.8°	0
44	1	R. L. L. R. M. L.	28.4	104.2°	0
62	1	R. L. L. R. M. L.	29.0	104.0°	+

in pneumonia, found in 40 consecutive cases of lobar pneumonia in human subjects that 5 showed displacement of the heart and trachea to the affected side and 22 elevation of the diaphragm on that side. In 105 cases of experimental pneumonia in dogs (Robertson's study<sup>14</sup>) there were 42 instances of visceral displacement toward the affected side.

**Summary and Conclusions.** Since 1921, several foreign clinicians have used therapeutic pneumothorax on the affected side in lobar pneumonia, with 47 recoveries and 3 deaths. Despite these optimistic reports we have found no published experimental data on this subject and we therefore undertook a study on animals in an effort to define and justify, if the evidence so warranted, the use of this treatment in man.

We have therefore produced lobar pneumonia in 36 dogs (Robertson method) 18 of which were treated by artificial pneumothorax and a like number used as controls. Observations on the course of the disease included clinical study, daily leukocyte determinations, blood cultures and roentgenograms. No other treatment was employed in either group and no attempt was made to control the behavior or feeding of the animals.

Both the clinical reports in the literature and our experimental study indicate that the introduction of air in the pleural cavity in proper amount on the affected side produces, temporarily at least, a picture comparable to the crisis in lobar pneumonia and achieves an artificial limitation of an otherwise self-limited disease. In addition to this, in the experimental animal, this treatment appears to have a favorable effect on the blood-stream invasion.

We are not prepared at this time to offer any explanation for the *modus operandi* of this method of treatment. We most emphatically



do not recommend artificial pneumothorax as a routine procedure in all cases of lobar pneumonia.

We believe that the clinical and experimental data which have been presented amply justify this treatment in selected cases of unilateral pneumococcic lobar pneumonia, with due regard for the danger of circulatory collapse incident to the cardiac and mediastinal displacement which may result from its use.

We agree entirely with Coghlan that lobar pneumonia is emphatically not the disease in which to acquire experience in the technique of artificial pneumothorax.\*

\* We have very recently had opportunity to treat by this method 1 patient, a male, aged 44, with lobar pneumonia, who was admitted December 2, 1933, to this hospital on Dr. Stengel's service, on the 3d day of the disease. On the following day, immediately before treatment, his temperature was 102.8° F., pulse 136, respirations 36 and the physical signs were those of complete consolidation of the left lower lobe. At 3 P.M. 400 cc. of air was administered. Profuse perspiration began almost immediately with an immediate fall in temperature which reached 99° F. at 9 o'clock the following morning. At this time the respirations were 24 and the pulse, which had dropped more slowly than the temperature, was 114. The physical signs of consolidation, which had become completely masked by the first treatment, reappeared at this time, indicating that the air had been largely absorbed. For this reason, another injection of 400 cc. of air was given. During that day the temperature reached 100° F. on one occasion. It then became normal. Within 7 hr. after the initial treatment, the patient was entirely comfortable and so remained. Examination of the sputum revealed pneumococcus Type 1. The blood cultures were sterile. Daily roentgenograms were comparable in all respects to those obtained in the experimental animals, similarly treated, with the exception that 400 cc. of air in this patient, who weighed 165 pounds, caused considerable cardiac and mediastinal displacement to the unaffected side. For some reason which we do not understand, a dog of 10 kg. will tolerate and actually require a much larger instillation proportionately than man. In man, the solid lobe or lung occupies a considerable amount of space in the pleural cavity despite the fact that it is more compressible than one would imagine. This case report with others will be the subject of another publication.

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## PNEUMOTHORAX TREATMENT OF PULMONARY TUBERCULOSIS.\*

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THE process of healing of tuberculosis is essentially the same in the lungs of patients treated with rest alone or when in addition pneumothorax is utilized. In the presence of pneumothorax recovery ensues not so much as a result of the collapse of the lung *per se*, but indirectly as a result of the better opportunity it offers a resistant individual for the fixation of the diseased parts by fibrosis and calcification. As a clinical corollary, one observes that the course of patients with relatively benign bilateral disease is more often influenced favorably in both lungs under the effects of pneumothorax treatment of the more actively diseased lung than is the course of patients with acute pneumonic phthisis that is limited to one lung. Indeed the tuberculous process may spread from a relatively limited focus and undergo caseation and cavitation in the presence of a pneumothorax. The general acceptance of partial compression with pneumothorax in the treatment of pulmonary tuberculosis, unfortunately an enforced procedure in most instances, also bespeaks a biologic rather than a mechanical factor as playing the predominant rôle in arresting the disease.

With pneumothorax, there results more or less contraction of the affected parenchyma, stasis of the blood and lymph flow and immobilization of the chest wall preventing further extension of the disease. After the pneumothorax is discontinued, the heart, mediastinum and diaphragm are almost invariably displaced to the diseased side and act as an additional tampon on the fibrotic and, not infrequently, bronchiectatic lung. This is apt to follow particularly fibro-ulcerative, pleuro-pulmonary tuberculosis that had been subjected to prolonged compression. In many favorable instances this constitutes the end result, the tuberculous process being held in check leading to clinical arrest of the disease. Under proper conditions, this mode of healing of pulmonary tuberculosis occurs also in patients who recover without the aid of collapse therapy.

In some patients, after pneumothorax has been discontinued and the lung has re-expanded, one obtains roentgenologic evidences of anatomic healing as shown by the disappearance of cavities and

\* This study was aided by a grant from the Board of Trustees of Montefiore Hospital.

absorption of tuberculous infiltration. Quite often, in these instances, there is little or no displacement of intrathoracic structures although the diseased lung may have harbored cavities of considerable size. This mode of healing is characteristic of benign, exudative types of pulmonary tuberculosis situated below the level of the clavicles. In this respect also it appears that pulmonary tuberculosis which responds to pneumothorax by resolution is of a type that behaves in a similar manner without the aid of pneumothorax. In other words, pneumothorax does not heal pulmonary tuberculosis. Its therapeutic value lies primarily in its ability to put the affected lung in an ideal state for natural processes of healing to take place. This explains why some patients, particularly those with fibro-ulcerative tuberculosis, require pneumothorax for a considerable duration and are liable to reactivations even after 3 or 4 years of collapse therapy, while others, particularly those with so-called infraclavicular tuberculosis, often get well after a comparatively short period of treatment.

**Indications for Pneumothorax.** In patients with minimal and moderately advanced pulmonary tuberculosis, pneumothorax is utilized most often in the treatment of uncontrollable hemorrhage. Otherwise, it is seldom used since it is the consensus of opinion that pneumothorax should not be instituted if there is a possibility of a natural involution of the disease. Unfortunately, one cannot foretell the course of the disease in specific instances. Extension is apt to take place to uninvolved parts of the same lung or, worse still, to the contralateral lung when least expected. Indeed, this may occur in the presence of retrogression of the primary seat of the disease.<sup>1</sup> According to recent views,<sup>2</sup> pulmonary tuberculosis does not begin in the apex but more often in the infraclavicular region, the process then progressing or retrogressing quite rapidly accompanied by few symptoms and physical signs. Obviously, such an evolution makes any attempt at prognostication a hazardous one.

Since there is a paucity of reliable criteria to enable the physician to gauge the course of the tuberculosis and since active disease in a young individual is a serious matter, it seems justifiable to institute pneumothorax as soon as it becomes apparent that the process in the lung is not showing signs of retrogression, particularly when cavities are present. A period of 2 or 3 months of observation with the patient under complete bed rest should suffice in the majority of instances. In patients with progressive pulmonary tuberculosis, the indication for pneumothorax is obviously a matter of urgent necessity. In the present state of knowledge of pulmonary tuberculosis and the *modus operandi* of collapse therapy, it appears that pneumothorax is the treatment of choice in young patients with relatively benign, infraclavicular or centrally located pulmonary tuberculosis if the disease does not show evidences of spontaneous resorption or cicatrization of the lesion under rest treatment.

Symptomatic improvement, particularly in the early months of treatment, is to be expected in many instances with bed rest alone although the disease in the lung may be little affected, indeed, may be progressing, simultaneously. This initial period of symptomatic improvement is apt to deceive the physician as well as the patient and pneumothorax is withheld as a consequence. Too often, subsequent recrudescence of the disease results in bilateralization or generalization of the tuberculosis and renders pneumothorax impracticable.

**Two-to-fifteen-year End Results in 324 Cases.** The results with pneumothorax depend on the character and extent of the pulmonary disease and on the collapse attained. This applies in a general way, but in specific instances neither factor can be estimated with any degree of accuracy. Indeed, after reviewing several hundred films, it seems that the supposedly measurable components of the pulmonary collapse are almost as immeasurable as are the factors that determine the individual's resistance to the disease. Unilateral tuberculosis in some patients, in spite of a satisfactory collapse of the lung, spreads to the unaffected lung and runs a fatal course. In others, with initially bilateral involvement, there is seen occasionally retrogression of the disease not only in the treated but also in the contralateral lung. Likewise, a pocket of air is apparently efficacious in one instance by localizing itself over an actively diseased area; a larger pocket of air in another patient may be ineffective because it collapses more of healthy than of diseased lung tissue. In any event, one is apt to judge the character of the collapse by the final outcome rather than by the results expected before the institution of the pneumothorax. At times, the outcome is such as to make one wonder as to the rôle the pneumothorax really played in influencing the evolution of the disease.

Our study of the results with therapeutic pneumothorax in pulmonary tuberculosis differs somewhat from similar studies made by others in as much as follow-up letters played a small part. Many of our patients who improved sufficiently had an opportunity to work part or full time in the Altro Shops, conducted by the Committee for the Care of Jewish Tuberculous. Here they were under medical and nursing supervision, the physical examinations being supplemented when necessary with roentgenograms. Of the patients who succumbed, 76 per cent did so in Montefiore Hospital. Many of the intermediate groups were readmitted on one or more occasions to the city hospital or the country sanatorium. A number of working patients were sent to the latter institution for vacations during the summer months. Several years ago a follow-up clinic was established where discharged patients are able to continue pneumothorax treatment and at the same time engage in various occupations. Our results are, therefore, to a considerable degree, based on first hand information of a homogeneous group of individuals whose

physical condition was ascertainable with some degree of accuracy. These end results have never before been collected for publication and are not included in Dr. Fishberg's work.

In the years 1916-1930, inclusive, 377 patients with pulmonary tuberculosis were treated with pneumothorax. With few exceptions, the disease was in an advanced stage. Information of the present condition of these patients is available in 324 instances, or in 86 per cent of the total number treated. Of this number, 13 patients are still receiving pneumothorax (2, since 1924; 2, since 1927; 1, since 1928; 3, since 1929; and 5, since 1930). Although some of the best results are to be found among the patients of this group, they are not included in estimating the final results. Likewise, 18 patients who have stopped receiving pneumothorax in the years 1931 and 1932 are also excluded. An interval of at least 2 years should elapse after pneumothorax is discontinued before one attempts to evaluate the results of the treatment.

The table summarizing the results with pneumothorax at Montefiore Hospital and Country Sanatorium is given with the full realization of the many shortcomings that enter presentations in which the personal equation plays such a decisive part. Nor does a multiplicity of tabulated data solve the problem. It is just as apt to confuse as to clarify matters. To reduce sources of error to a minimum, the material is arranged according to predominance of unilaterality or bilaterality of disease and according to whether or not the pneumothorax, irrespective of its character, could be maintained for a period of at least 3 months (Table 1). The majority of the patients who received treatment for less than 3 months were essentially instances of frustrated attempts to establish a pneumothorax either as a result of pleural adhesions (predominantly unilateral group) or as a result of the *ultimum refugium* type of patient (predominantly bilateral group) in whom collapse of the more actively diseased lung was tried on the principle that there was nothing to be lost by the attempt. Rarely was there anything gained. That a considerable number of our patients fell into the hopeless group may be gathered from the fact that no less than a third of all the fatal instances occurred within 6 months of the time of induction. Needless to say, comparatively few of those who received pneumothorax for more than 3 months sustained complete collapse of the affected lung.

Pneumothorax for at least 3 months was given to 143 patients with predominantly unilateral pulmonary tuberculosis. Of these, approximately 28 per cent are clinically arrested and 13 per cent are improved to a degree that a number are working or able to work. It should be noted that among the improved group of patients the sputum of 8 became negative and that some patients remained well for as long as 15 years. They are not included among the clinically arrested group because there was insufficient proof that

such was the case. Our positive results in patients with predominantly unilateral pulmonary tuberculosis in whom some degree of pneumothorax could be established constitutes roughly about  $\frac{1}{3}$  of the patients treated. The stationary group of patients includes many who were symptomatically benefitted by the treatment but who subsequently needed further hospitalization or additional

TABLE 1.—TWO- TO FIFTEEN-YEAR END RESULTS IN 324 CASES, 1916-1930.

Condition.*	No.	Predominantly unilateral pulmonary tuberculosis.		Predominantly bilateral pulmonary tuberculosis.	
		3 mos. or more	Less than 3 mos.	3 mos. or more	Less than 3 mos.
Still receiving PNX . . . . .	13	3 mos. or more	Less than 3 mos.	3 mos. or more	Less than 3 mos.
Discontinued 1931 and 1932 . . . . .	18				
Clinically arrested . . . . .	44	41	1	2	0
Sputum negative . . . . .	35				
No sputum . . . . .	5				
Sputum unknown . . . . .	4				
Improved . . . . .	23	19	0	4	0
Sputum negative . . . . .	8				
Sputum positive . . . . .	2				
No sputum . . . . .	7				
Sputum unknown . . . . .	6				
Stationary . . . . .	18	14	2	0	2
Progressive . . . . .	11	4	1	5	1
Uncertain . . . . .	5	4	1	0	0
Dead† . . . . .	186	61	42	31	52
Within 3 mos. of induction, 30					
Within 6 mos. of induction, 59					
Within 1 yr. of induction, 88					
Within 2 yrs. of induction, 141					
Within 5 yrs. of induction, 174					
Total . . . . .	318	143	47	42	55
* Bilateral PNX, not analyzed	3				
† Non-tbc. causes, not analyzed	3				
	324				

collapse procedures. There are relatively few patients in the progressive group for the reason that not many are alive after a lapse of 2 years. Sixty-five per cent of all the patients treated had effusions of varying degree detectable roentgenologically during the course of treatment. In about 40 per cent of all the patients treated, the effusion occupied  $\frac{1}{3}$  or more of the pleural cavity. The presence of a

pleural effusion seems to have had no effect on the final outcome. Among the 143 patients with predominantly unilateral pulmonary tuberculosis who received pneumothorax for 3 months or more, the incidence of pleural effusion among the patients whose disease became arrested and among the patients who died was approximately the same, 80 to 78 per cent. These comparative findings support the belief that pleural effusions in the course of the pneumothorax should not be aspirated unless pressure symptoms or other urgent indications arise. In several instances when a partial pneumothorax was followed by an effusion, the prognosis was distinctly improved as a result. More often, however, our statistics as to the ultimate effects of such effusions notwithstanding, their appearance caused

TABLE 2.—COMPARATIVE RESULTS WITH THERAPEUTIC PNEUMOTHORAX IN 1926 CASES, REPORTED BY 10 DIFFERENT OBSERVERS.

Source.	Type of material.	Period of observation, years.	Number.	Living.	Per cent.	Dead.	Per cent.	Results of total number, per cent.
Münchbach <sup>3</sup>	PNX practicable	2-9	475	273	57	202	43	Fully able to work, 37.
Graveesen <sup>4</sup>	Simple unilateral PNX, 6 mos. or longer	2-12	140	60	43	80	57	Able to work, 39.
Roloff <sup>5</sup>		2-12	262	*	60	*	40	Sputum negative, 45.
Maendl <sup>6</sup>	Satisfactory or incomplete effective collapse; exclusive of those under treatment	2-12	172	85	49	87	51	Fully able to work, 36.
Peters <sup>7</sup>		2-14	167	79	47	88	53	Condition satisfactory, 30.
Arni <sup>8</sup>	Successful PNX	2-14	170	46	27	124	73	Fully able to work, 21.
Zinn and Siebert <sup>9</sup>	Partial or total PNX	2½-15	183	77	42	106	58	Healed, 15.
Hurrell <sup>10</sup>	Successful PNX induced	3-10	99	27	27	72	72	Well, 17.
Schröder <sup>11</sup>	Av. duration of PNX, 8½ mos.	3-15	115	50	44	65	56	Healed, 37.
Rubin	Predominantly unilateral; PNX 3 mos. or more	2-15	143	82	57	61	43	Clinically arrested, 29; sputum negative, 30.
Total	More or less PNX induced	*	1926	779	47	885	53	

premature abandonment of pneumothorax treatment. About 16 per cent of all the effusions were purulent in nature. The prognosis of patients with pyopneumothorax, with few exceptions, is a gloomy one.

The results in this series when compared with those reported from other institutions (Table 2), reveal a striking similarity in accomplishment. The minor variations are due to differences in the types of patients treated and interpretations of results rather than to any specialized modifications in treatment. Of major importance is the interval that is allowed to elapse between the time of discontinuation of pneumothorax treatment and the assessment of the results. The longer this interval the worse appear the final results. After a lapse of at least 2 years, about 25 per cent of the patients are in good condition without tubercle bacilli in the sputum and

able to work; about 25 in fair condition and about 50 per cent dead. These percentages, as is true of statistics in general, do not represent the actual facts. Obviously, one cannot expect permanent benefits of the treatment in patients with bilateral pulmonary tuberculosis or when pleural adhesions prevent collapse of the cavities in the lung. Yet, this applies to a large number of patients treated with pneumothorax. Symptomatic improvement is the most that can be expected under such conditions. Equally deceptive, on the other hand, are the unusually favorable results obtained in patients with unilateral disease in whom the pneumothorax caused complete collapse of the cavities and in whom the treatment could be maintained for several years and discontinued voluntarily. Such selected groups of patients constitutes a relatively small minority of all the patients treated. The results are significant in so far as it demonstrates the value of collapsing tuberculous cavities. It is very likely that with the change in views regarding the indications for pneumothorax treatment, in time, many more patients will fall into the latter group.

**Conclusions.** Pneumothorax improves the condition of many patients with pulmonary tuberculosis who otherwise would very likely not have done as well. Quite infrequently, collapse of the lung, even when partly successful, helps the individual to arrest the progress of the disease so that he becomes economically rehabilitated and is able to lead a normal although somewhat sheltered life. The individual, however, is still tuberculous and subject to all the vicissitudes of the disease. At the present time in comparatively few does it result in full clinical recovery in a sense that the tuberculous process undergoes absorption or complete fibrosis and calcification. It is hazardous to speak of cure, under any condition, when reactivations are liable to occur at any time during the life of the patient. Pneumothorax attempts to treat pulmonary tuberculosis, not the tubercle bacillus. For this reason, if for no other, such a measure directed locally in the treatment of this condition is necessarily limited in its sphere of action.

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## THE BEHAVIOR OF THE DIAPHRAGM AFTER PHRENICO-EXAIRESIS.

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THE therapeutic effects of phrenicoexairesis in pulmonary tuberculosis, irrespective of the character, extent, and location of the lesion, depend on the changes produced by the procedure in the position and function of the corresponding hemidiaphragm. Successive examinations of the paralyzed muscle are therefore of considerable prognostic value, and often serve to explain the failures as well as the successes of the treatment.

In chronic pulmonary phthisis varying degrees of impairment of the normal function and, occasionally, complete immobility of the hemidiaphragm on the more diseased side are not uncommon. Even more frequently we meet with a position of the hemidiaphragm higher than normal on the side of the contemplated operation. Occasionally, the upward retraction, resulting from fibrosis and contraction of the lung, is greater than the rise which could be expected from a radical phrenic nerve interruption.

Although there are no definite criteria by which the results of phrenicoexairesis can be foretold, these abnormalities yield much valuable information in regard to the possibilities of an effective postoperative rise of the hemidiaphragm. Not only for this reason, but also for comparative purposes is it important that the function and position of the diaphragm should always be determined before operation.

**Examination of the Diaphragm.** Various landmarks have been proposed whereby to measure the postoperative rise of the diaphragm on the roentgenogram. Most of them are unsuitable because their positions vary too much with different examinations. The method employed in the 170 cases studied in this series consists in determining the difference between the positions of the two halves of the diaphragm by means of horizontal lines drawn through the highest points of the domes before operation, and adding the figure thus obtained to, or subtracting it from, the difference in the positions of the two domes after operation, depending upon whether the hemidiaphragm on the operated side was originally lower or higher than on the contralateral side. The rise may also be measured by the difference in the distance between the tip of the transverse process of the first thoracic vertebra and the highest point of the dome of the hemidiaphragm, before and after operation (Figs. 1a and 1b). Although subject to error, owing to the inconstant heights of the

normal and of the paralyzed hemidiaphragms in films taken at different times, these measurements are more accurate than recording the elevations in interspaces and fingerbreadths.

On fluoroscopic examination the paralyzed hemidiaphragm is either immobile, or presents a paradoxical motion (a rise of the diaphragm instead of a descent with inspiration, and the opposite with expiration). The latter may be absent on ordinary respiration, but may be brought out in many cases by the sniffing test and the Bittorf<sup>1</sup> test. The sniffing test is performed by having the patient inspire forcibly through the nose with the lips tightly closed; and the Bittorf test, by a strong inspiratory effort with the lips and the nostrils tightly closed. The result in both tests is a rise of the hemidiaphragm with inspiration, and a descent with expiration. Frequently the paradoxical motion produced by these tests is more marked than the paradoxical motion on ordinary respiration. They may, however, be absent even when the paralysis is complete.

TABLE 1.—RELATIONS BETWEEN ACTUAL, MINIMUM, MAXIMUM AND AVERAGE RISES OF THE DIAPHRAGM, AND LENGTH OF NERVES EVULSED IN 138 CASES.

Rise of diaphragm in cm.	Length of evulsed nerve in cm.							Total.	Per cent.
	2.5-5.5	6-9	10-15	16-20	21-30	31-38	Over 38		
No rise	6	3	1	1	..	1	..	12	8.8
1- 2	..	1	..	..	1	..	..	2	1.4
2- 3	2	3	2	3	3	3	..	16	11.7
3- 4	4	10	11	2	4	2	1	34	24.8
4- 5	1	3	5	4	8	4	..	25	18.2
5- 6	1	2	6	3	7	4	..	23	16.8
6- 7	1	1	1	..	6	1	1	11	7.8
7- 8	..	1	3	..	1	2	1	8	5.6
8- 9	..	..	1	..	3	..	..	4	2.8
9-10	..	..	..	..	2	..	..	2	1.4
11-12	..	..	..	..	..	..	1	1	0.7
Average rise	3.87	3.79	4.54	3.85	5.16	4.67	5.02		
Minimum rise	2.00	1.25	2.00	2.00	1.20	2.00	3.10		
Maximum rise	6.60	7.50	8.75	5.00	9.00	7.70	7.50		
Average rise rt.	4.31	3.54	4.35	3.89	4.70	5.85	4.55		
Average rise lt.	3.00	4.07	4.67	3.73	5.55	4.50	5.50		
Maximum rise rt.	6.60	4.20	7.20	5.00	9.00	7.70	6.00		
Maximum rise lt.	3.10	7.50	8.75	5.00	8.75	7.00	7.50		

I. *Changes in the Position of the Diaphragm.* The effect of phrenic nerve interruption on the position of the corresponding hemidiaphragm has been studied in a series of 170 cases. In 12 cases the position of the hemidiaphragm could not be determined on account of opacity of the lung field, and 20 cases were not included for various other reasons.

In 12 (8.7 per cent) of the 138 cases thus available for study, no rise of the hemidiaphragm occurred (Table 1). Some authors have reported a much greater proportion of such cases. Frank and Miller<sup>2</sup>

found no ascent in about 30 per cent of 85 cases. Cooper<sup>3</sup> reported no rise in 36.8 per cent of 103 cases. Others, however, found no rise, in the presence of paralysis, in a very small proportion of cases. Edwards<sup>4</sup> observed it only three times in 98 cases, and Broga and Welles<sup>5</sup> in 3 out of 72 cases.

In 4 cases the failure of the hemidiaphragm to rise was due to the fact that no paralysis of the muscle was produced by the procedure. In 2 the hemidiaphragm showed complete immobility throughout a period of observation of 3 months and 5 years, respectively. In 1 case the hemidiaphragm was completely immobile before operation. One case presented a marked paradoxical motion during a period of observation of 6 months. In 3 cases the function of the hemidiaphragm was not noted, but no rise had occurred 9 months, 1 year and 2 months, and 1 year and 4 months, respectively, after operation. In 1 case, crushing of the nerve produced no result. Five months later an exaeresis of 31.25 cm. was performed. One month later there was no rise, with an immobile hemidiaphragm.

No relation could be established between failure of the hemidiaphragm to rise and the extent of nerve resection, in view of the fact that other cases with the same lengths of nerve evulsed showed elevations from 2 to 7.5 cm. The paralyzed hemidiaphragm may remain permanently at its preoperative level irrespective of the length of nerve evulsed. In 1 case no rise occurred after resection of 20 cm., and in another case of 31.3 cm.

The average and maximum rises of the hemidiaphragm vary considerably in different series of cases. The figures reported by various authors cannot be compared because of a lack of standard methods of measurements, and of data concerning the time between the date of operation and the date of final observation.

Of our cases 126 showed rises between 1.2 and 9 cm., with an average rise of 4.5 cm., not including 1 case in which the elevation reached 11.3 cm.

According to Thomsen,<sup>6</sup> Zadek and Sonnenfeld,<sup>7</sup> and others, there is no relation between the length of nerve evulsed and the degree of ascent of the hemidiaphragm. On the other hand, it is claimed that the probability of attaining a good rise grows with the extent of nerve removed, and that the average elevation is greater following evulsion than simple phrenicotomy. Felix<sup>8</sup> found an average rise of 3.7 cm. on the right and 2.5 cm. on the left after simple phrenicotomy, and 7.6 cm. on the right and 5.9 cm. on the left following exaeresis, and Alexander<sup>9</sup> an average rise of 2.15 cm. after simple phrenicotomy and 4.25 cm. after exaeresis. Sultan<sup>10</sup> stated that frequently, but not regularly, the height attained by the paralyzed hemidiaphragm is in direct proportion to the length of nerve removed.

An analysis of our cases shows, first, that in individual cases

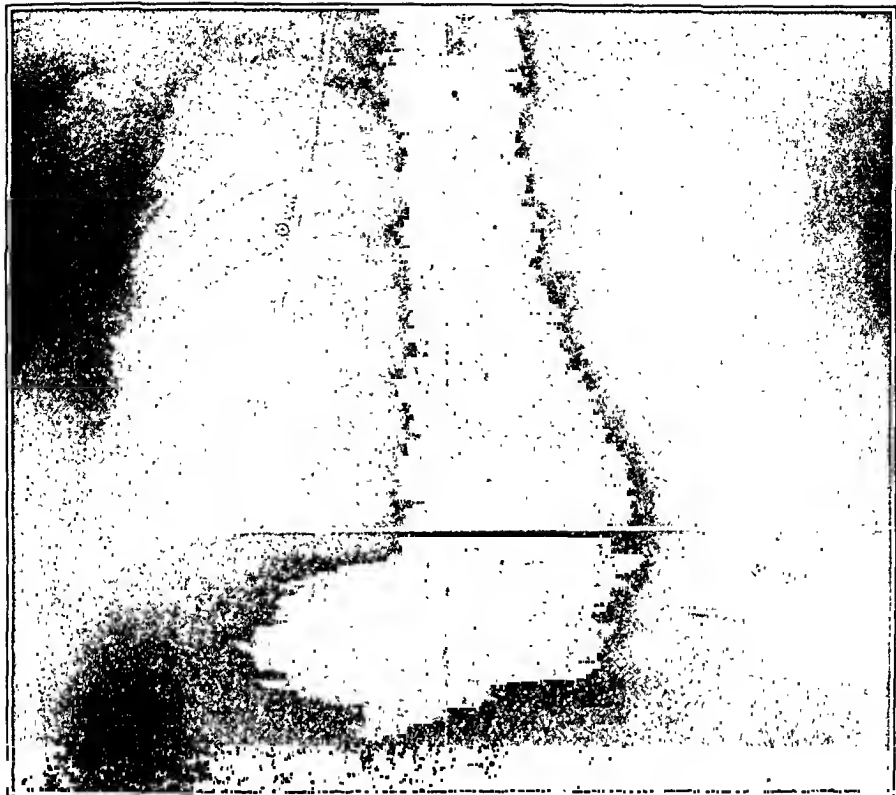


FIG. 1a.—Right hemidiaphragm before operation 3 cm. higher than left.

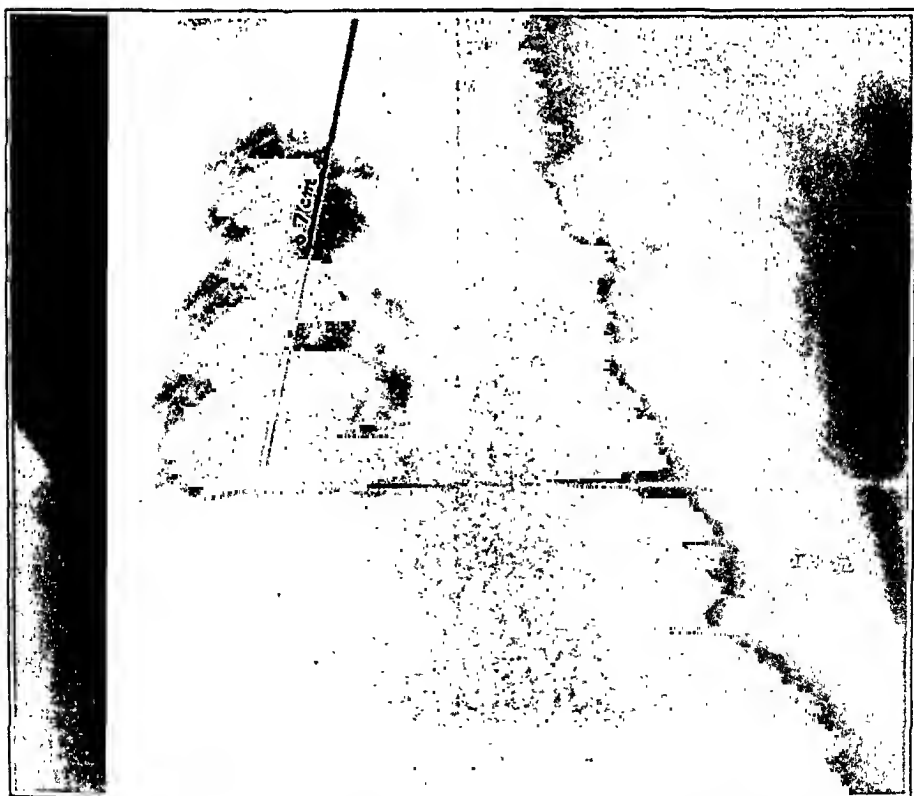


FIG. 1b.—Right hemidiaphragm after operation 5.3 cm. higher than left. Actual rise 2.3 cm.



higher rises may occur with resection of nerve lengths corresponding to simple phrenicotomy than with exairesis up to the whole nerve, second, that the average rises in the nerve length groups as classified in Table 1 do not permit the deduction that there is a direct relation between nerve length and degree of rise. If, however, the cases are divided into those with resection of nerve lengths less than 10 cm., and over 10 cm., the latter group shows a slightly higher average, but not great enough to justify any generalization.

Extremely high rises are not frequent. Sultan<sup>10</sup> has seen an elevation of the right diaphragm 11 cm. higher than the left, and of the left diaphragm 9 cm. higher than the right. Puder<sup>11</sup> reported a case in which the hemidiaphragm rose to the second rib. Campbell<sup>12</sup> found the maximum rise 8 cm. on the right and 6 cm. on the left. Maendl and Schwartzmann<sup>13</sup> saw an elevation of 11 cm. in 100 cases. Matson<sup>14</sup> found a rise of 8.5 cm. on the right side 1 year after operation, and of 13 cm. on the left side 2 years after operation, in a series of 150 cases. The maximum elevation noted by O'Brien<sup>15</sup> in 500 cases was 9 cm. Cooper<sup>3</sup> observed rises of 7 and 8 cm. Frank and Miller<sup>2</sup> saw elevation up to the third rib in some of their cases. In our cases the maximum rises were 9 cm. on the right side in 2 cases, 6 months, and 3 years and 5 months after the operations, and 11.5 cm. on the left side, 2 years and 4 months after operation.

Saucrbruch,<sup>16</sup> Felix,<sup>8</sup> Alexander,<sup>9</sup> Sultan,<sup>10</sup> Davies,<sup>17</sup> Campbell,<sup>12</sup> Moore<sup>18</sup> and others have noted that the rises on the right side are greater than on the left side, the average differences varying between less than 1 cm. and 4 cm. The explanation is that on the right side the ascent of the hemidiaphragm is aided by the upward push of the liver, while on the left side the heart hinders the rise. Thomsen<sup>6</sup> and Edwards,<sup>4</sup> on the other hand, have not been able to corroborate this observation, and have found very little, if any, differences between the two sides. In our cases, contrary to the generally reported findings, the average rise on the right was 4.3 cm., and on the left side 4.7 cm. In only 3 of the groups (Table 1) were the average and maximum rises greater on the right than on the left side. It was also found that whereas rises of 5 to 9 cm. constituted about 28 per cent of the right-sided cases, they were noted in about 43 per cent of the left-sided cases.

The probability of obtaining a rise of the hemidiaphragm is somewhat greater for the right than for the left side. Cooper<sup>3</sup> found that the number of right-sided cases with a rise was about 16 per cent higher than of the left-sided cases. In our cases the advantage of the right over the left side was only about 8 per cent.

The maximum elevations of the paralyzed hemidiaphragm are reached at varying periods of time after operation. Rises up to 7 cm. in from 1 week to 1 month occur frequently. In many cases the highest rise is reached within the first 6 months. Frequently, the rise increases for much longer periods of time. However, taking our

whole series of cases, it appears that the elevation bears no consistently direct relation to the time elapsed after operation (Table 2).

TABLE 2.—RELATIONS BETWEEN LENGTHS OF TIME ELAPSED AFTER OPERATION, AND ACTUAL, MAXIMUM AND MINIMUM RISES OF THE DIAPHRAGM IN 125 CASES.

From date of operation.	Number cases.	Rise of diaphragm in cm.						
		Less than 2.5	2.5-5.0	5.0-7.5	7.5-10.0	11.25	Maximum rise.	Average rise.
Less than 3 mos.	18	1	12	4	1	..	6.0	4.2
3-6 mos.	12	..	10	2	..	..	5.6	4.1
6-9 mos.	20	2	10	6	2	..	9.0	4.8
9-12 mos.	18	2	10	6	..	..	6.6	4.1
1-2 yrs.	41	4	18	15	4	..	8.8	4.8
2-3 yrs.	12	2	6	4	..	..	7.2	4.3
3-4 yrs.	4	..	1	1	2	..	9.0	6.8

Case with rise of 11.25 cm. not included.

In some cases we have observed the opposite phenomenon, namely, a gradual descent of the hemidiaphragm following a continuous rise, in the presence of complete paralysis of the muscle. We have seen no mention of this in the literature. In some instances the decreases were slight, and could, perhaps, be explained by differences in the positions of the two halves of the diaphragm during different exposures. In 6 cases, however, the descent varied between 2 and 3 cm., and was noted on successive examinations. The interval between the time when the maximum rise and the drop were noted was between 3 and 7 months, and in 1 case, 1 year. A fully satisfactory explanation is not offered. The descent may be the forerunner of a restoration of normal function. In the majority of the cases, however, such lengths of the nerve were evulsed which very rarely are unsuccessful in producing complete and permanent paralysis. It is probable that decrease of the intraabdominal pressure as a result of weakening of the abdominal musculature from progressive emaciation and asthenia is an important factor in the mechanism. Similarly, no satisfactory explanation is available for the observation of varying degrees of elevation of the paralyzed hemidiaphragm at different times. In some of these cases the changes were of such an extent that they could not be ascribed to differences in the depths of the inspirations during different exposures.

**Discussion.** From the foregoing analysis it appears that the post-operative position of the paralyzed hemidiaphragm is not determined to any important degree, if at all, by the length of nerve evulsed. Primarily, it is the result of the combined action of the suction force of the negative intrathoracic pressure, and of the upward push of the positive intraabdominal pressure. This mechanism, however, is supplemented and modified by the changes which take place in the structure of the muscle, and by the pathologico-anatomical character of the pleuropulmonary lesion.

Failure of the paralyzed hemidiaphragm to rise and limitation of the rise have been ascribed to fixation of the basal portion of the lung and, especially of the costophrenic sinus, by pleural adhesions. It is doubtful, however, that this plays the important rôle that has been assigned to it. According to Kahn,<sup>19</sup> the degree of rise depends by far more on the intraabdominal pressure. The higher the latter, the higher the hemidiaphragm will rise. In asthenic individuals with a poorly developed musculature, and a slight amount of intraabdominal fat the pressure is very slight and a high elevation does not occur, except in a small number of cases in which there is a well developed abdominal musculature in the presence of asthenia.

In a large number of our cases phrenicoexairesis was performed because of a completely adherent lower lobe in artificial pneumothorax. Yet, in the great majority of these cases satisfactory, and even maximum rises, occurred. We have also observed cases with definite obliteration of the costophrenic angle, in which the diaphragm ran from within outward and upward in a more or less straight line, where, however, a continuous rise up to 5 cm. took place.

It is probable that the character of the lesion of the lower lobe is of greater significance in determining the ascent of the hemidiaphragm. Massive infiltration and marked fibrotic changes, which make the lung rigid and unyielding, will prevent or restrict the rise. Compensatory emphysema of the lower lobe in cases of chronic upper lobe lesions will act similarly. The most important, however, of the various factors which interact in determining the postoperative position of the hemidiaphragm, is the rapidity and intensity with which the pulmonary lesion contracts, as healing takes place, and the muscular fibers of the diaphragm undergo degeneration and atrophy. As a result of the traction and contraction of scar tissue, the intrathoracic pressure may attain high negative values whereby the hemidiaphragm may be pulled upward with great force. Degeneration and atrophy of the paralyzed muscle converts it into a thin, yielding connective-tissue membrane which offers less and less resistance to the intraabdominal and intrathoracic pressures, and to the contraction of the lung, unless counteracted by factors which prevent or limit the ascent.



II. *Functional Changes.* For the study of the functional changes of the paralyzed hemidiaphragm there were available 112 cases with periods of observation of 3 months and longer. The number of fluoroscopic examinations made in each case varied between 2 and 14, as follows:

Number of cases.	Number of examinations.
38	2
13	3
16	4
9	5
11	6
18	7
3	8
2	9
1	10
1	14

The conditions noted were, first, lasting immobility; second, immobility which gave place to paradoxical motion; third, lasting paradoxical motion, and, finally, paradoxical motion which was replaced by immobility. In 6 cases the hemidiaphragm eventually regained its normal function.

In 52 (46.4 per cent) of the cases, the hemidiaphragm became immobile soon after operation, and remained fixed for periods of observation varying between 3 months and over 5 years.

In 14 (12.5 per cent) of the cases, the immobile hemidiaphragm developed paradoxical motion. The time after operation when the immobility was last observed was from 2 weeks to 4 months after, in 10 cases; and from 1 year and 2 months to 1 year and 7 months in 4 cases. The first observation of paradoxical motion was made from 1 to 10 months later, the average being about  $3\frac{1}{2}$  months.

Three cases showed complete immobility before operation. In 1 of these the hemidiaphragm remained fixed without at any time becoming elevated; in 2 paradoxical motion set in 1 month and 9 months, respectively, after operation; and in both, elevation of about 4 cm. took place, in 1 before and in the other after the paradoxical motion developed.

In 2 cases there was a return to normal function after an initial period of immobility.

Immobility, as here spoken of, refers to complete absence of respiratory excursions of the hemidiaphragm on ordinary and even deep breathing. The sniffing and Bittorf tests, however, may show paradoxical motion. Out of the 52 cases with persistent fixation, the tests were performed in 22, and were positive in 12 (54.5 per cent). In the 14 cases in which immobility was followed by paradoxical motion, the tests were positive in 13 (92.8 per cent). Comparing the two groups, it was found that, generally, the intensities of the tests were greater in the second group, and that they increased after the setting in of paradoxical motion.

In 41 (36.6 per cent) of the 112 cases, there was paradoxical motion from the start. In 3 of these the function became normal, and 4 cases are not included because the periods of observation were less than 2 months.

In 23 of the 41 cases (51.2 per cent), the paradoxical motion persisted and was positive at the termination of observation from 3 months to 3 years after operation. In 11 (26.8 per cent) the hemidiaphragm eventually became immobile. The paradoxical motion, in the latter cases, persisted for 1 to 10 months, or at an average of less than 4 months in 9 cases, and for over 1 year in 2 cases, after operation. The hemidiaphragm was found fixed from 2 to 18 months, or at an average of about 11 months, after operation. The sniffing and Bittorf tests were investigated in 16 of the 23 cases and in 10 of the 11 cases, and were found to be positive in all the former, and in 80 per cent of the latter. These findings, in connection with the results in the group where paradoxical motion followed a period of fixation, showed that although these tests are positive in a large proportion of cases with an immobile hemidiaphragm, they are practically always present when there is paradoxical motion on ordinary respiration.

**Discussion.** Immobility, either from the beginning or setting in after a varying period of paradoxical motion, may be considered the rule after phrenic nerve interruption, with or without a rise of the paralyzed hemidiaphragm. It was found in 63 of 100 of our cases. Frank and Miller<sup>2</sup> noted immobility of the hemidiaphragm in 58 (85.3 per cent) of 68 cases.

Complete fixation has been ascribed to the presence of pleural adhesions. It appears to the writer that such an explanation alone cannot be sustained. Pleural adhesions of the basal portion of the lung, so pronounced as to interfere completely with the mechanism which produces paradoxical motion, should also prevent a rise of the hemidiaphragm, or restrict it greatly. As a matter of fact, only 4 out of 52 cases in this group presented no rise. The other cases showed an average rise which was approximately the same as the general average rise. The predominating cause of immobility of a paralyzed and atrophied hemidiaphragm is, essentially, the same as that which determines the degree of elevation, namely, the character and the retractile capacity of the pulmonary process. When the retractile capacity of the lung as a result of massive infiltration and pleural adhesions is not sufficient to allow free play to the suction force of the intrathoracic pressure and to the upward push of the intraabdominal pressure during inspiration, the hemidiaphragm will remain fixed. Where immobility gives place to paradoxical motion it must be assumed that there has occurred a change in the retractile capacity of the lung in the sense of an increased elasticity, corresponding to healing and fibrosis. Another explanation for the latter phenomenon is that the diaphragm atrophies gradually.

The farther the conversion into a lax, fibrous membrane has progressed, the more easily it is acted upon by the intrathoracic and intraabdominal forces. The change from paradoxical motion to immobility is to be explained by the assumption that the lung becomes more and more inelastic and unyielding, and that, in addition, there occurs the development of more extensive and firm adhesions.

Paradoxical motion is produced by the upward suction of the increasing negative intrathoracic pressure during inspiration, supplemented by the increasing intraabdominal pressure, acting upon a hemidiaphragm which has lost its tonus. Theoretically, the more marked the paradoxical motion, the more it presupposes comparative freedom from adhesions and, especially, an elastic retractile lower lobe. Practically, however, it is not true in all cases, nor even in the majority of cases. As a matter of fact it is difficult, if not impossible, to explain on the basis of the factors which are supposed to determine the presence or absence of a rise of the hemidiaphragm, and of paradoxical motion, why the latter is marked in some cases and absent in others.

Although in individual cases no relation between the degree of rise and the presence of lasting paradoxical motion can be established, this group as a whole shows a higher average rise than the other groups, and than the general average rise. There also does not appear to be any relation between the length of nerve evulsed and paradoxical motion or immobility.

The degree of paradoxical motion on ordinary respiration, and by the sniffing and Bittorf tests, bears a fairly definite proportional relation to the time elapsed after operation, due to the increasing degeneration of the muscle fibers. It is borne out by an analysis of our cases, which showed a higher average rise, by about 3 cm., in the group with moderate and marked paradoxical motion than in the group in which it was classified as of slight degree. Only 1 of the cases with paradoxical motion of a marked degree showed no rise of the hemidiaphragm during 8 months after operation and evulsion of 7.5 cm. of the nerve.

**Summary.** The changes in the function and position of the hemidiaphragm after phrenic nerve interruption have been studied in a series of 138 cases.

The characteristic effects of phrenicoexairesis on the diaphragm are a rise of the muscle into the thoracic cavity, immobility, and paradoxical motion.

In a small proportion of cases the hemidiaphragm remains permanently at its preoperative level, even after evulsion of a sufficient length of nerve to produce complete and lasting paralysis.

In the majority of cases, there occurs a rise, which in the largest number of these is associated with immediate or subsequent lasting immobility of the hemidiaphragm.

Failure of the paralyzed muscle to rise, the degree of rise, immobility and paradoxical motion, all depend largely if not entirely on the character of the pulmonary process, especially of the lower lobe, and on the extent and character of pleural adhesions, especially of the basal portion.

The mechanism by which all these conditions are determined, however, requires further physiologic and pathologico-anatomical study.

The effect of phrenicectomy on the pulmonary lesion is determined largely by these changes. A study of the behavior of the phrenicectomized hemidiaphragm in every case is therefore important from a prognostic standpoint.

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### THE EFFECT OF PREGNANCY ON THE INSULIN REQUIREMENT OF THE DIABETIC.

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THERE are conflicting views regarding the effect of pregnancy on the insulin requirement of the diabetic. This is due largely to the infrequency of pregnancy in the diabetics who require insulin; there was not a single instance of diabetes in 27,567 consecutive patients confined in the City of London Maternity Hospital.

The purpose of this paper is to clarify existing misunderstanding in regard to changes in the insulin need and to formulate, if possible, certain rules, the adoption of which, we believe, will minimize the risk to the mother and child.

Since the observations of Carlson and Drennan<sup>1</sup> an improving tolerance during the last months of pregnancy has been attributed to insulin supplied by the pancreas of the fetus. That this may actually occur is beyond doubt. One of Wilder's<sup>2</sup> patients became diabetic, requiring insulin in the first trimester of pregnancy while in the last trimester the insulin was discontinued, to be resumed after the nursing period was over. The third case in the same publication behaved in a similar fashion. Gray and Feemster<sup>3</sup> report a great economy of insulin after the 8th month of pregnancy. At necropsy a remarkable hypertrophy and increase in the number of islets in the baby's pancreas were found. Others<sup>4-11</sup> report a reduced insulin need or improved food tolerance in the last trimester of pregnancy.

When evidences of a rapidly gaining tolerance present themselves there is no alternative but to reduce the insulin or increase the diet. The question arises: is the abnormal output of insulin by the fetal pancreas a compensatory affair, the result of an unusual demand—poorly controlled diabetes in the mother—if so, can we prevent this hyperfunction with its possible injury to the child by keeping the maternal blood sugar normal?

This was the aim in our 6 cases. Even though the renal threshold is lowered in pregnancy,<sup>12</sup> every attempt was made to prevent glycosuria. In none was there evidence of assistance from the fetal pancreas. We are inclined to attribute this to the exact control of the diabetes and believe that if we had been less fortunate in this respect that compensatory activity of the fetal pancreas would have been more likely.

It is generally agreed that carbohydrate tolerance is lost during the first 3 months of pregnancy, the period of greatest metabolic readjustment. This has been our experience also. Judging from the literature, it is apparent that the second trimester is freest from complications. In our cases the insulin requirement remained stationary during this, the period of greatest qualitative fetal development. Unlike the results of others referred to above, we noted that each patient during the final trimester, the one of greatest increase in body mass, required increasing quantities of insulin. Two patients reported by Collens and Shack<sup>13</sup> illustrate this change. Bowen and Heilbrun<sup>14</sup> in reporting 5 cases showed evidence of loss of tolerance in 3. Their review of 43 cases from the literature revealed an increased demand for insulin in 28 and a decrease in 10. Of Peckham's<sup>4</sup> cases, 3 (6, 9 and 12) lost tolerance during pregnancy. This was true of 1 patient reported by McIlroy, Hill and Pillman-Williams.<sup>15</sup> Others<sup>2,7,16-35</sup> report instances of loss of tolerance in the last trimester. It would appear that more lose tolerance than gain it during pregnancy.

We have collected 78 pregnancies complicating diabetes from the literature and have added the 6 reported in this paper. These cases comprise all of those, to the best of our knowledge, in whom the insulin requirement was sufficiently clear to enable us to determine the effect of pregnancy upon it. The results of this survey are presented in Table 1.

TABLE 1.—THE EFFECT OF PREGNANCY ON THE DIABETIC'S TOLERANCE AS JUDGED BY CHANGES IN THE AMOUNT OF INSULIN REQUIRED.

The diabetic's tolerance during pregnancy.	No. of cases.	Per cent total.
I. Impaired (no evidence of hyperactive fetal pancreas)	47	55.9
II. Unchanged (possibly some assistance from fetus)	16	19.1
III. Improved (evidence of hyperactive fetal pancreas)	21	25.0
	84	100.0

**Case Reports.** CASE 1.—Mrs. T. A., aged 38, height 63 inches, weight 117 pounds (53 kg.), had diabetes since 1924. Insulin was begun in April, 1925. The patient gave a history of 1 previous pregnancy. The baby died at 2 weeks of age. Except during the first pregnancy, there had been no disturbance in menstruation. Her mother had glycosuria of undetermined cause. The only past illness was scarlet fever in childhood. Her general physical condition was excellent. The pregnancy began in September, 1927. Before this time her daily dosage of insulin was 40 units, at the end of the 3d month it was 82 units, at the end of the 6th month 82, and at the end of the 9th month 98. Following a normal delivery there were severe insulin reactions and the insulin requirement dropped at once to 44 units. The baby weighed 9 pounds, 6 ounces.

CASE 2.—Mrs. M. (Physiatric Inst. Case 385), aged 30, with recognized diabetes since 1919, gave a family history (father) of diabetes. Insulin was begun in 1923. Her weight was normal and showed no unusual change. Prior to the pregnancy in 1924 she required 72 units of insulin daily, at the end of the 3d month 78 units, at the end of the 6th month 78, and at the end of the 9th month 100. Subsequent to delivery the requirement was 72 units.

CASE 2.—Second pregnancy. Prior to the second pregnancy in 1927, the daily insulin need was 72 units, at the end of the first trimester 76, of the second trimester 76, and of the third, 100. Her standard dosage following delivery proved to be 70 units. Severe insulin reactions followed both deliveries, making imperative reductions below the usual dosage for this patient for several days.

CASE 3.—(Physiatric Inst. Case 1914.) Mrs. N., aged 20, with a history of diabetes since 1924 and amenorrhea until 1926, became pregnant in June, 1929. Insulin had been started in 1924 and the daily dosage prior to pregnancy was 75 units. Unfortunately, we have no record of her insulin throughout the pregnancy, but at the end of the 9th month it was 94 units. Following delivery insulin reactions were prominent and the insulin was reduced to 40 units. The insulin requirement remained below her normal requirement while she nursed her baby.

CASE 4.—(Physiatric Inst. Case 2317.) Mrs. M., aged 32, had been treated for diabetes since 1923. She was married in September, 1929, and became pregnant in March, 1932. There had been no disturbance in menses since beginning insulin in 1923. Before pregnancy she required 40 units of insulin daily, at the end of the 3d month 48, of the 6th month 48, and of the 9th month 100. When standardized following delivery but while she was nursing the baby, her insulin need was 35 units. The diet remained constant throughout.

CASE 5.—Mrs. J. H. R., aged 30, height 62 inches, weight 89 pounds (40 kg.), gave a family history (maternal) of diabetes. Diabetes and pregnancy were both recognized in September, 1931. Past illnesses were diphtheria, mumps and measles in childhood. Her physical condition was good except for undernutrition. Prior to the pregnancy glycosuria had never been found though tested for regularly, the patient being a laboratory technician. She did not need insulin before pregnancy; at the beginning of the 2d trimester she required 4 units daily; of the 2d trimester, 6 units and of the 3d trimester, 8. Following delivery the blood sugar remained at the lower border of normal. The insulin was discontinued and until the present (June, 1933) there has been no return of hyperglycemia or glycosuria. The mother did not nurse the baby. The baby's weight at birth was 6 pounds, 14 ounces.

TABLE 2.—INSULIN REQUIREMENT DURING EACH TRIMESTER, COMPARED WITH THAT BEFORE AND AFTER PREGNANCY.

Case.	Daily insulin requirement (units).					Remarks.
	Before pregnancy.	At end of 3d mo.	At end of 6th mo.	At end of 9th mo.	After delivery.	
1	40	82	82	98	44	
2	72	78	78	100	72	First pregnancy
2	72	76	76	100	70	Second pregnancy
3	75	?	?	94	40	Nursed baby
4	40	48	48	100	35	Nursed baby
5	0	4	6	8	0	

**Comments.** Six successful pregnancies in 5 diabetics are reported. In all but 1 (Case 5) in whom the menses had been normal, menstruation had previously returned under insulin and diet treatment.

In each case, changes in the insulin requirement throughout pregnancy behaved in a similar fashion and in each case a prompt decrease in the insulin need followed delivery. The diabetes was not more severe after than before the pregnancies. The 2 patients who nursed their babies needed less insulin during the nursing period than before pregnancy. This is in agreement with the observation of Macleod, Markowitz and Simpson.<sup>36</sup>

The babies are all living and well.

Changes in diet probably played a small part in changing the insulin requirement. The total calories were not increased though a higher carbohydrate content was allowed and was continued after confinement—after the insulin had been reduced. There was no unusual gain of weight in any of these patients.

**Summary.** Though the number of cases is too small from which to form absolute conclusions, we believe that:

1. Exact control of the diabetes throughout the course of pregnancy will prevent abnormal demands on the pancreas of the fetus.

2. By adopting this practice the insulin requirement increases in the first trimester, remains constant in the second, increases in the third and decreases suddenly after delivery. In consequence, it would appear that the time of greatest danger from ketosis is in

the first and third trimesters; and from hypoglycemia, immediately following delivery; whereas if the second trimester is entered free from complications there is little likelihood of trouble during this midperiod.

3. Differing from the behavior of the uncomplicated diabetic, there is in our experience a paradoxical behavior of the insulin requirement in the last trimester of pregnancy: when the insulin is increased fully to cover the needs of the diabetic, there is not a gain but a loss in tolerance; we regard a gain in tolerance at this time as unfavorable for the child as it is due in all probability to an abnormally active fetal pancreas.

4. Pregnancy under ideal conditions and treatment does not permanently impair the diabetic's tolerance.

5. Diabetes *per se* is not a contraindication to pregnancy.

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## RHEUMATIC FEVER IN PIEDMONT VIRGINIA.

## I. INCIDENCE AND CLINICAL MANIFESTATIONS.\*

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THE apparent relationship of climate to variations in the incidence and course of rheumatic infection has commanded much deserved attention in the medical literature of the past half century. For any disease which is so obviously influenced by extrinsic physical factors should offer peculiar advantages for analysis. As early as 1859 Hirsch<sup>1</sup> studied the global distribution of rheumatic fever and noted its relative infrequency in tropical and subtropical countries. These observations have in the intervening years become generally confirmed by investigators from both old and new hemispheres.

The purpose of this study has been to determine, as far as is practicable, the incidence of rheumatic disease for the central piedmont section of Virginia and to note in particular the occurrence and severity of its various forms. It is fully realized that statistical values founded upon hospital admissions alone do not offer an accurate index to the morbidity of a disease which is so commonly treated in the home. Community studies, though more exact, presuppose facilities which are but rarely available. It is thought, however, that a fairly accurate representation of the occurrence of the *various manifestations* of rheumatic disease is afforded by detailed observation of a number of individual cases.

The extensive literature relative to the subject has been more recently reviewed by Paul.<sup>2</sup> It would appear that accurate information as to the true climatological incidence and severity of rheumatic disease in *all of its manifestations* is not readily obtainable from the majority of epidemiological surveys. In most instances uniform definitive criteria for the selection of cases have not been employed or not specifically stated. Increasing evidence points to a variability in the character of rheumatic disease for different geographical areas. It is, therefore, apparent that the incidence of a single

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rheumatic manifestation, such as arthritis, cannot be considered in any or all localities as an index to the occurrence of the disease as a whole. Likewise, the frequent omission of pediatric cases from the statistical study of a disease to which children are particularly susceptible would seem an obvious fault.

The concept of rheumatic fever as a general bodily infection with widespread clinical and pathologic forms has been, through repeated observations, satisfactorily established. Cheadle,<sup>3</sup> in 1888, recognized the association of arthritis, pleurisy, endocarditis, tonsillitis, chorea, exudative erythemata and subcutaneous nodules, urging a broader visualization of the disease. Three years before, Howard<sup>4</sup> emphasized the frequency of pulmonary manifestations and assembled 109 cases from the current literature in which pneumonia, pleurisy, or bronchitis had been observed. Extensive involvement of the vascular system, aside from intrinsic heart lesions, has more recently been described by Klotz,<sup>5</sup> by MacCallum,<sup>6</sup> and by Von Glahn and Pappenheimer.<sup>7, 8</sup> In a recently published monograph, Coburn<sup>9</sup> stresses the importance of a wider consideration of the "Rheumatic State—a mosaic of disease patterns."

Although the clinical and pathologic manifestations of rheumatic infection are numerous and widely varied, but few of these forms when occurring singly are characteristic of the disease. Thus arthritic disturbances, Sydenham's chorea, or a certain pattern of circulatory phenomena must be present, alone or in combination with other associated signs, before a diagnosis may be established. It would appear that in some localities these essential diagnostic figures of rheumatic disease may exist in so mild a form as commonly to escape recognition, even as in others the severity and variability of their associated manifestations often confuse the issue. Arthritis may be caused by a number of known and unknown factors, and endocarditis occurs in the absence of rheumatic infection. Continued investigations afford increasing evidence of the probable rôle of streptococcus infection as the causative agent in rheumatic disease. If true, the kinship of that condition to scarlet fever and follicular tonsillitis cannot be denied. Yet these conditions, although paralleling rheumatic fever in distribution and severity, may not be included in statistical studies of that disease unless other definite rheumatic manifestations are demonstrated in the same individuals. Likewise acute nephritis, although not proven to be characteristic of rheumatic disease, has long borne an implied association with that condition partly as a true rheumatic manifestation and partly on account of a supposed clinical and climatologic similarity. Its admission rate for the University of Virginia Hospital (0.74 per cent), based on criteria similar to that utilized below for rheumatic fever, is recorded here in the hope that further parallel observations may be stimulated. Unless associated with characteristic rheumatic manifestations, cases of

acute nephritis have been excluded from the subsequent analysis of rheumatic fever cases.

To clear away any possible doubt as to the type of case under consideration we have confined our observations to patients diagnosed as having acute or recurrent rheumatic arthritis, valvular heart disease of rheumatic origin, rheumatic carditis with or without diagnosable valvular disease and Sydenham's chorea. We have studied 200 persons so diagnosed in the medical and pediatric wards of the University Hospital, during the 6-year period from June 1, 1926, to June 1, 1932. Of this number 158 (92.5 per cent) were listed as residing in Virginia. Nine of the remaining 15 persons lived in the adjacent state of West Virginia; 6 came from more distant localities. Thus a great majority were from the central piedmont section of Virginia, with an altitude of from 500 to 1500 feet.

TABLE 1.—RHEUMATIC FEVER (ACUTE, RECURRENT AND CARDIAC FORMS AND CHOREA).

(University Hospital, University, Va., June 1, 1926, to June 1, 1932.)

	Admissions.	Rheumatic disease.	Rate, per cent.
Hospital . . . . .	40,536	200	0.48
Medical and pediatric wards . . . .	14,758	200	1.35
Medical wards alone . . . . .	10,686	165	1.54
Pediatric wards alone . . . . .	4,073	35	

Cases have been analyzed with particular reference to the frequency and degree of the manifestations of the rheumatic syndrome in this region. Preliminary studies concerned with a comparison of the incidence and character of rheumatic infection for the piedmont and tidewater sections of Virginia would seem to indicate marked differences in the forms of the disease for these localities. Analysis of a second group of 42 patients from tidewater Virginia (Norfolk), collected over exactly the same period and arranged similarly by Dr. W. B. Martin, of Norfolk, offers interesting contrast in regard to incidence and occurrence of the various rheumatic manifestations.

In our series the admission rate for rheumatic disease as calculated for medical and pediatric admissions and medical admissions alone is given in Table 1.

For the sake of comparison, the average yearly admission rate for rheumatic disease as obtained for medical patients alone (admissions to adult medical wards) has been computed (Table 2), modified from the reports of Faulkner and White,<sup>10</sup> of Longcope,<sup>11</sup> and of Harrison and Levine.<sup>12</sup> The percentage obtained for central piedmont Virginia (1.54) would appear to indicate that the disease occurs as commonly in this locality as in Baltimore, for Longcope in the selection of medical cases employed criteria similar to those utilized in this study. Yet a single previous figure quoted from Richmond, Virginia, by Harrison and Levine indicates a far

lower frequency. This discrepancy is due partially to the failure to include all rheumatic manifestations in the Richmond figure and partially to probable actual difference between the frequency of rheumatic fever in eastern and central Virginia. This latter explan-

TABLE 2.—RHEUMATIC DISEASE: REGIONAL DISTRIBUTION.

(Adapted from Faulkner and White, and Longcope.)

Locality.	Av. yearly med. adm.	Av. yearly adm., rh. fever, chorea.	Rate, per cent.
San Francisco Hosp., Calif. . . . .	1,255	47.0	3.75
Sacred Heart Hosp., Spokane, Wash. . . . .	1,384	42.0	3.03
Univ. Hosp., Iowa City . . . . .	1,537	38.0	2.40
Univ. Hosp., University, Va. . . . .	1,781	27.5* †	1.54
Bellevue Hosp., N. Y. . . . .	25,915	375.0	1.50
Johns Hopkins Hosp., Baltimore . . . . .	1,723	23.0*	1.37
Peter Bent Brigham Hosp., Boston . . . . .	2,480	31.0	1.30
Hosp. of Univ. of Penna., Phila. . . . .	1,518	17.0	1.20
Univ. Hosp., Omaha, Neb. . . . .	760	5.0	0.70
Charity Hosp., New Orleans . . . . .	5,349	28.0	0.52
Jefferson Hosp., Philadelphia . . . . .	4,085	19.0	0.50
Barnes Hosp., St. Louis . . . . .	1,338	6.5	0.47
Los Angeles County Hosp. . . . .	13,614	55.0	0.44
Baptist Mem. Hosp., Memphis, Tenn. . . . .	3,037	6.5	0.20
Univ. Hosp., Augusta, Ga. . . . .	2,500	2.0	0.08

(Adapted from Harrison and Levine, 1924.)

Locality.	Av. yearly med. adm.	Av. yearly adm., rh. fever.	Rate, per cent.
Peter Bent Brigham Hosp., Boston . . . . .	1,593	30.0	1.85
Barnes Hosp., St. Louis . . . . .	1,319	14.0	1.04
Galveston Hosp., Galveston, Tex. . . . .	875	7.0	0.84
Johns Hopkins Hosp., Baltimore . . . . .	1,911	14.0	0.73
Charity Hosp., New Orleans . . . . .	6,632	18.0	0.30
Richmond, Private practice, Dr. VanderHoof . . . . .	1,332	1.0	0.07

\* Includes cases of acute and recurrent rheumatic fever, rheumatic heart disease and chorea.

† Our figures added for sake of comparison.

TABLE 3.—HOSPITAL INCIDENCE OF VALVULAR HEART DISEASE, RHEUMATIC ARTHRITIS AND CHOREA.

(In Central Piedmont and Tidewater, Virginia.)

June 1, 1926, to June 1, 1932.	University Hospital, University, Va.		Hosp. of St. Vincent de Paul, Norfolk, Va.	
Total admissions . . . . .	40,536		26,455	
Total rheumatic fever . . . . .	No. cases, 200	Adm. rate %, 0.48	No. cases, 41	Adm. rate %, 0.15
Incidence major manifestations.	No. cases.	Per cent.	No. cases.	Per cent.
Valvular heart disease . . . . .	138	69	22	53
Rheumatic arthritis . . . . .	158	79	14	34
Chorea . . . . .	34	17	5	12

ation is well supported by a rheumatic fever incidence in the piedmont section of Virginia of over 3 times that in tidewater Virginia (Table 3). Notable variations within this state itself thus occur, a situation almost certainly present in other sections, witness Los Angeles (rate 0.44 per cent) and San Francisco (rate 3.15 per cent) (Table 2). It cannot be assumed, therefore, that a given frequency

figure for one locality necessarily applies to another of approximately the same latitude though perhaps only 200 miles distant. However, as regards the admission rates listed for other hospitals, any exact comparison is impossible, since it is doubtful whether or not cases of valvular heart disease of rheumatic origin have been included under the heading of rheumatic fever (Table 2). At least, as far as Boston is concerned, rheumatic heart disease has been said to be twice as frequent as in this section of Virginia.<sup>13</sup>

In our series, patients were distributed according to race and sex as noted in Table 4. The figures obtained are in harmony with the observations of other investigators. The slight but definite trend to a higher incidence in the female is a commonly expressed, though unexplained, feature of the disease. The proportion of white to colored patients of 6.7 to 1 is a ratio which becomes 1.7 to 1 when corrected for the number of white to colored (4 to 10) admissions at this hospital. These figures would seem to indicate that rheumatic fever is decidedly less common in the negro than in the white, an observation previously noted by Longcope, who did not, however, give the ratio of white to colored admissions for Johns Hopkins. This contention is further supported by 3 rheumatic heart disease studies<sup>14, 15, 16</sup> in 2 southern states, although here again the assumption is not warranted that rheumatic heart disease necessarily represents a fair index of racial susceptibility to rheumatic fever. Even so, the inference is decidedly stronger than the single contrary contention of Atwater,<sup>17</sup> who has implied a high negro susceptibility on the basis of mortality statistics for acute rheumatic fever.

TABLE 4.—RACE AND SEX INCIDENCE IN 200 CASES OF RHEUMATIC DISEASE.  
(From Central Piedmont Virginia; University Hospital, University, Va.)

	Males.	Females.	Totals.
White . . . . .	85	89	174
Colored . . . . .	11	15	26
Totals . . . . .	96	104	200

NOTE.—White to colored ratio 1.7 to 1 when corrected for hospital admission frequency.

(From Medical Clinic, Johns Hopkins Hospital; Longcope.)

White . . . . .	59	55	114
Colored . . . . .	14	14	28
Totals . . . . .	73	69	142

As already stated, each of the patients included in this study presented evidences of rheumatic arthritis, heart disease of rheumatic origin, or chorea at the time of observation or previously. An analysis of arthritic manifestations in the 200 cases is recorded in Table 5. The percentage of joint involvement as observed for this portion of Virginia would appear to be considerably higher than that noted by Longcope<sup>11</sup> for Baltimore and vicinity.

TABLE 5.—JOINT MANIFESTATIONS IN 200 CASES OF RHEUMATIC FEVER.  
(From Central Piedmont Virginia.)

Arthritis.	No. cases.	Percentage (of all cases).
Arthritis, total . . . . .	158	79.0
Arthritis, at time of admission . . . . .	81	40.5
Initial attack . . . . .	50	25.0
Recurrent attack . . . . .	31	15.5
Arthritis, history only . . . . .	77	38.5
Single attack . . . . .	47	23.5
Recurrent attack . . . . .	30	15.0
Total, single attacks . . . . .	61	30.5
Rheumatic disease, no evidence of arthritis . . . . .	42	21.0

In our 158 patients presenting evidence of arthritis, pain on joint motion was by far the most common symptom, although varying markedly in severity and often unaccompanied by appreciable swelling. The duration of joint symptoms in a single attack seldom exceeded 10 days except in prominent instances although recurrent attacks were noted in a relatively large number of cases. In only 3 persons were symptoms confined to a single joint. Forty-two patients were included in this series of 200 cases despite the fact that there were obtained no evidences from history or examination of past or present attacks of rheumatic arthritis. Of these, valvular heart disease was observed in 31 instances; in the remaining 11, Sydenham's chorea.

The occurrence of the several types of valvular heart disease observed in the 200 patients under consideration is described in Table 6. The high percentages derived attest the danger of serious cardiac involvement in the rheumatic disease of this section. Longcope<sup>11</sup> has noted a similarly high incidence of cardiac manifestations for the region of Baltimore and vicinity, and is of the opinion that for that locality, heart disease may be considered the chief form of the disease.

TABLE 6.—INVOLVEMENT OF THE HEART VALVES IN 200 CASES OF RHEUMATIC DISEASE.

Classification.	No. cases.	Percentage.
Valvular heart disease . . . . .	138	69.0
Mitral stenosis and insufficiency alone . . . . .	81	40.5
Aortic disease alone . . . . .	18	9.0
Pure aortic regurgitation . . . . .	14	7.0
Aortic regurgitation and stenosis . . . . .	4	2.0
Mitral and aortic disease . . . . .	39	19.5
Total mitral disease . . . . .	120	60.0
Total aortic disease . . . . .	57	28.5

Active rheumatic carditis was thought to be present at the time of observation in 106 cases, 54 of these falling in the group listed in Table 6, and 52 instances in which valvular disease of the heart could not be demonstrated. The criteria employed in a determina-

tion of activity for each case were these clinical and electrocardiographic evidences currently accepted as significant.

Sydenham's chorea had occurred or was observed in 34 of the 200 cases in this series (17 per cent). Of these 18 were associated with typical rheumatic fever, 5 with valvular heart disease, and in 11 cases chorea occurred alone.

**Comment.** The influence of some unknown factor in climate upon the incidence and course of rheumatic fever seems to have been satisfactorily established. Likewise, it would appear that the several manifestations of the disease vary in occurrence and severity for different localities. For example, Longcope has indicated that the cardiac syndrome commonly over-shadows the arthritic manifestations of the disease in Baltimore. Our own experience is essentially the same. Arthritis either by history or observation was recorded in 79 per cent of our patients (Table 5) (77 per cent, Longcope). Further, a low incidence of arthritis but a relatively high incidence of heart disease is seen in the figures for tidewater Virginia (Table 3). Here the recorded incidence of arthritis is definitely less than that either in piedmont Virginia or Baltimore, but the heart disease frequency remains comparatively high. An apparently low incidence of rheumatic arthritis therefore need not mean an equally low frequency of rheumatic heart disease. The best indication of the comparative frequency of rheumatic heart disease in piedmont and tidewater Virginia will be afforded by a careful survey of the school children of these two sections. Such a study is now in progress.

**Summary.** Two hundred instances of rheumatic disease, observed during a 6-year period at the University of Virginia Hospital, have been studied in an effort to determine the approximate incidence of the disease as a whole and to note particularly the relative occurrence of its various manifestations.

It would appear that rheumatic fever is of frequent occurrence in central piedmont Virginia, where it is 3 times as common as in the tidewater section of the same state. The arthritic forms of the disease, although mild and of such short duration as to suggest that they may at times escape detection, are relatively frequent and tend to recur in a fairly high percentage of cases. Serious and permanent damage to the heart is evidenced in a surprisingly large number of persons with rheumatic fever.

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## A HEMORRHAGIC ERUPTION OF THE MOUTH AND THROAT IN THE RHEUMATIC STATE.

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SINCE the publication of Libman's classification of the endocarditides in 1923, the occurrence of petechiæ, especially those with white centers, has been associated with subacute or acute bacterial endocarditis. Libman<sup>1</sup> stated that petechiæ are found rarely in rheumatic fever and only as part of purpuric eruptions. Another lesion, however, heretofore undescribed, occurs frequently in the oral and pharyngeal mucous membranes in cases of chronic rheumatic endocarditis. It is a recurrent eruption, and has no diagnostic or prognostic significance in relation to the development of subacute bacterial endocarditis. While its appearance is not strictly limited to chronic rheumatic endocarditis, it is during the course of this infection that we have observed it most often during the past five years. Because the lesion is essentially one of the mucous membranes of the mouth and throat, and because it is unrelated to the presence of bacterial endocarditis or purpura, we regard it as a non-embolic hemorrhagic enanthem.

The eruption is seen in the mucous membranes of the cheeks, soft palate, sublingual region, fauces, uvula, the tip and borders of the tongue, and the tonsils. By far the most frequent site is the buccal mucosa, especially anterior and inferior to the opening of Stensen's duct. It consists of a circular, unelevated, deep red spot, varying in size from a pin point to 2 mm. in diameter. It may be present



alone or in groups of two or more. More rarely, one sees a shower of myriad pin points or a mosaic of larger spots distributed over the entire surface of the uvula or soft palate. In the buccal mucous membranes, pin point or slightly larger spots, occurring singly or in groups are the most frequent. Their color is usually the crimson of a fresh hemorrhage, but they may assume a darker, bluish hue. White centers have never been observed. The spots disappear or fade considerably after 24 hours. They are then very often promptly replaced by a new crop at the same site or elsewhere. Diffuse eruptions on the uvula or soft palate may persist for 2 weeks or more.

The comparative frequency of this lesion in patients with rheumatic infection and in apparently non-rheumatic subjects has been studied. Although it is seen rarely in the latter group, it is in chronic rheumatic heart disease, where rheumatic infection is recurrently or continuously active, that the enanthem makes its most frequent and repeated appearance. In a recently studied group of 19 cases of rheumatic valvular disease of the mitral and aortic valves, examined at biweekly intervals for 4 months, hemorrhagic spots were found in 9 cases at the initial examination and in a total of 13 cases during the period of study. Of 29 cases without rheumatic valvular disease, chosen at random for control, spots were found in only 1 case. Further observation on unselected cases revealed that the spots occur frequently during the course of a group of infections generally considered as indicating the presence of the rheumatic state. These include especially acute rheumatic fever, rheumatoid arthritis and erythema nodosum. It has been seen also in acute follicular tonsillitis and other acute upper respiratory infections, including otitis media. Other significant associations have been subacute bacterial endocarditis and congenital heart disease with unexplained fever, and cases of transient arthralgia and myalgia. The conditions in which the enanthem was seen unaccompanied by any evidence of rheumatic infection were malnutrition, diabetes mellitus, chronic vascular nephritis and mumps. Infrequently it has been found in apparently healthy children, and once in a case of idiopathic epistaxis in a healthy adolescent boy. Petényi<sup>2</sup> has described a similar constellation of hemorrhagic spots as a prodromal sign of measles before the appearance of Koplik spots.

The histologic features of the lesion are shown in Figs. 1 and 2. The specimen is one of buccal mucosa containing a spot. It was removed during an exacerbation of acute carditis in a male patient, aged 29, who had had chronic rheumatic mitral and aortic endocarditis for 10 years. In Fig. 1 there is a circumscribed area of hemorrhage which corresponds to the clinically observed lesion. It lies in the edematous squamous layer of epithelium. In all the sections examined there is increased vascularity of the epithelial and sub-epithelial layers. Fig. 2 illustrates the changes in the bloodvessels.

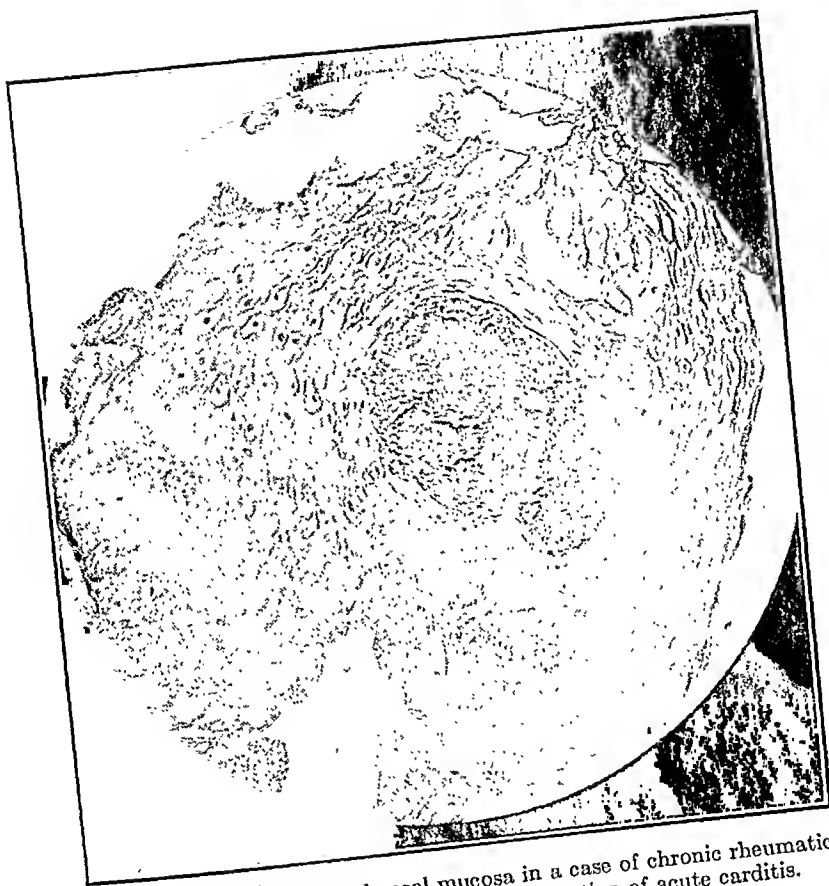


FIG. 1.—A hemorrhagic spot in buccal mucosa in a case of chronic rheumatic aortic and mitral endocarditis during an exacerbation of acute carditis.



FIG. 2.—Vascular lesion in subepithelial tissue in vicinity of hemorrhage shown in FIG. 1.

These are thickening of the media and intima, endothelial proliferation and, in many vessels, a shelflike protrusion of the hyperplastic intima into the lumen. (Pathologic study by Dr. A. A. Eisenberg.)

**Discussion.** The nature of the diseases with which the above described enanthem most frequently is associated and the setting in which it appears, lead us to suspect that it is closely related to infections of the rheumatic type. Transient bacterial infections without clinical manifestations are now known to occur, and have been detected by chance positive blood cultures, positive skin tests with streptococcal filtrates and serologic reactions. The great frequency with which the lesion has been observed in chronic rheumatic heart disease in particular, and its occurrence in other conditions included under the generic term, the rheumatic state, further suggest that the spots may indicate repeated occult infections. In patients with chronic rheumatic heart disease, the relationship of the spots to upper respiratory infection and climatic conditions links them more closely to the rheumatic state. The enanthem is strikingly more frequent during the early spring and winter months when respiratory infections and acute exacerbations of carditis are endemic. With the advent of hot dry weather, the incidence of spots is relatively small. However, no constant relationship between their frequency and the activity of rheumatic infection, as indicated by the generally accepted criteria, such as fever, leukocytosis, sedimentation rate, joint pains, prolonged *P-R* intervals, etc., has been established.

The pathologic changes in the bloodvessels in the vicinity of the lesion are not distinctively rheumatic. Neither cellular infiltration nor fibrosis is present. Nevertheless, the arterioles present features which cannot be considered normal. It should be recalled in this connection that Klotz,<sup>3</sup> Pappenheimer and von Glahn,<sup>4,5,6,7</sup> and others have described the arterial lesions of rheumatic fever in other locations. Fraser<sup>8</sup> has described characteristic rheumatic lesions in the tissues of the pharynx and in the faucial and lingual tonsils.

The absence of specific rheumatic lesions and the occurrence of the enanthem in patients who have no other evidence of rheumatic infection lead us to defer a final evaluation of its significance until the concept of the rheumatic state has been further elaborated.

**Conclusions.** 1. An enanthem consisting of an eruption of hemorrhagic spots, was observed in the mucous membranes of the mouth and throat of patients with rheumatic heart disease.

2. It was also noted in other diseases included in the concept of the rheumatic state, and in relatively few patients in whom there was no apparent rheumatic infection.

3. It has been seen more frequently during the course of rheumatic heart disease than in any other condition and the seasonal peak of its frequency in this disease coincides with that of acute upper respiratory infections and carditis.

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## THE NEURALGIAS OF THE HEAD AND FACE.\*

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*Trigeminal Neuralgia.* The most common neuralgia of the face occurs in the distribution of one or more branches of the trigeminal nerve. Because of the characteristic type of pain, often described as stabbing, lancinating, knifelike and momentary, which follows the course of the anatomical distribution of the 5th nerve and is induced by cold currents of air, lightly touching the face or by movements of the lips or jaw, it is readily diagnosed and correctly treated, either temporarily by alcoholic injection of the appropriate branch of the 5th nerve, or permanently by intracranial section of the sensory root of this nerve somewhere central to the Gasserian ganglion. This pain is often erroneously ascribed to sinusitis and diseased teeth for which prolonged treatment is often instituted without the slightest effect. Spontaneous remissions for weeks or months occur for no apparent reason. Following a coryza or acute sinusitis the tic may reappear, frequently more severe and of longer duration than in former attacks.

*Atypical Facial Neuralgia.* Occasionally associated with this trigeminal tic douloureux is the so-called atypical facial neuralgia which is believed to be of sympathetic origin. It has been confused with Shuder's neuralgia, but cocainization or injection of the sphenopalatine ganglion gives no amelioration of the pain. The pain of an atypical facial neuralgia is more constant, lasting for hours or days, varying in intensity and developing exacerbations of intense sharp pain. This neuralgia is described as a deeply seated, burning, throbbing, aching pain in the temporal, zygomatic, maxillary and nasal regions, behind the eye, in the nose, the cheek, the gums, and at times just behind the ear.

Flothow,<sup>1</sup> Mixer and White<sup>2</sup> were the first to offer relief to

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patients suffering from this atypical neuralgia when they ablated the sympathetic chain in the region of the first, second and third thoracic ganglia. Recently Fay<sup>3</sup> has shown that the network of sympathetic fibers in the region of the carotid bifurcation plays a rôle in the causation of this neuralgia, which may explain the partial relief at times obtained after ablation of the upper cervical sympathetic ganglion. Apparently these sympathetic painful impulses may be conveyed to the brain not only by the cervicothoracic chain into the spinal cord and then cephalad, but also from the carotid plexus to the vagus and then to the brain. An illustrative case may elucidate the symptoms of both trigeminal tic douloureux and atypical facial neuralgia.

CASE 1.—Mrs. M. C., aged 48, entered Lane Hospital in September, 1929, complaining of facial neuralgia for 20 years. At first there were small flashes of sharp pain in the right upper incisor tooth which had been crowned. She endured these transient attacks for 3 years when the crown was removed and the nerve killed. This treatment gave freedom from pain for 2 years. Then a stabbing pain appeared in the right temple, cheek and upper jaw as "terrible electric shocks." It seemed to start in the upper lip and cheek and was induced by touching these parts or the inside of the cheek, nose or gum, or by drinking cold water. Occasionally the lancinating pain spread to the lower jaw or to the forehead. She also complained of a deep-seated pain in the right zygomatic region in or behind the eye, and deep in the frontotemporal region. This aching pain at times was independent of the ticlike pain. Teeth were removed but she remained incorrectly diagnosed for 15 years. Attempts were then made to give relief by peripheral alcoholic injections.

In September, 1929, the sensory root of the 5th nerve was completely avulsed by Dr. Emile Holman, producing anesthesia over the whole distribution of the 5th nerve and completely curing the ticlike "electric shocks."

In July, 1931, she returned because of right occipital headache and burning of the right side of her cheek, tongue and lips, these areas having the sensation of being scalded. Lightly rubbing the right eye caused a severe burning, drawing pain. There was a tingling sensation of the right face and the same severe aching pain in the zygomatic and right maxillary region.

Injection of the sphenopalatine ganglion with novocain had no effect, but a novocain block of the right sympathetic chain at C<sub>7</sub>, T<sub>1</sub> and T<sub>2</sub> relieved these complaints nor could they be induced during the period of sympathetic block by rubbing the eye. An alcoholic injection of the sympathetic chain was then made at the level of C<sub>7</sub>, T<sub>1</sub> and T<sub>2</sub>. A severe neuralgia of the arm and upper chest persisted for 6 weeks. Since the alcoholic injection (1½ years) she had been free of her occipital headache. The burning in the lips, temple, tongue and cheek disappeared but the tongue has a mild feeling of being "scalded." Neither rubbing the eye nor placing cold objects on the face causes the burning sensation. She no longer feels the tingling in the face, and the aching pain in the zygomatic and maxillary areas has disappeared.

There have been 5 patients with this combination of trifacial tic douloureux and atypical facial neuralgia. The tic pains were relieved by interruption of the 5th nerve. Three were relieved of the atypical neuralgia by alcoholic interruption of the upper thor-

acic sympathetic chain, but in 2 no amelioration of symptoms was secured from the sympathetic block. One of the latter, who also recently had the sympathetics in the region of the carotid bifurcation removed as well as the superior cervical ganglion, was only partially relieved of her symptoms.

*Sphenopalatine and Vidian Neuralgia.* The symptoms of atypical facial neuralgia are similar to those of sphenopalatine (Sluder's) and vidian neuralgia and it may be that a common factor will be found as the cause of these neuralgias. In some of the atypical neuralgias cocainization or injection of the sphenopalatine ganglion has brought no relief. Nor has washing of the sinuses been of any help. Vail<sup>4</sup> feels that sphenopalatine and vidian neuralgia are the same, since the irritation in the vidian nerve from a sphenoid inflammation could extend forward to the sphenopalatine ganglion and its terminal orbital, nasal and palatine branches as well as backward to the geniculate ganglion of the 7th nerve through the great superficial petrosal nerve and through the great deep petrosal nerve to the internal carotid sympathetic network.

Sluder's neuralgia is described as pain in the root of the nose, in and about the eye, in the upper jaw and teeth extending beneath the zygoma to the ear, and frequently to the occiput, neck, shoulder and arm.

Vidian neuralgia is characterized by pain in the nose, face, eye, ear, head, neck and shoulder which comes in severe attacks and which has been relieved, as have cases of sphenopalatine neuralgia, by treating disease in the sphenoid sinus.

Perhaps, as Vail believes, too little attention has been given to sphenoiditis as the cause of these neuralgias. Certainly with syndromes (atypical facial neuralgia, sphenopalatine neuralgia and vidian neuralgia) so similar, one should thoroughly investigate the sphenoid sinus before attempting to bring relief by other means.

*Migraine.* Although attacks of migraine may be initiated by fatigue, menstruation, food idiosyncrasy and other exciting causes, the underlying neurologic mechanism which produces the hemicrania and such other disturbances as hemianopsia, paresthesias, ophthalmoplegia, unilateral pallor or flushing, lacrimation and nasal congestion would indicate involvement of the sympathetic nervous system. Many "remedies" have been tried, but none seems to bring relief in every case. Recently Dandy<sup>5</sup> reported complete relief in 2 patients for  $2\frac{1}{2}$  and  $6\frac{1}{2}$  months after removal of the inferior cervical and first thoracic sympathetic ganglia. Penfield<sup>6</sup> felt that sympathectomy in the cervical region, which not only removed the chain but the plexus on the carotid and vertebral arteries, was insufficient. From experimental work with his associate, Chorobski,<sup>7</sup> and from the work of Davis and Pollock,<sup>8</sup> he concluded that referred pain in the head, such as in migraine, was of sympathetic origin from fibers accompanying the fibers of the trigeminal nerve, joining them

central to the Gasserian ganglion and following the ophthalmic branch of this nerve in particular. In 1 case of migraine Penfield secured relief for 3 years after complete cranial sympathectomy including intracranial division of the medial or ophthalmic group of posterior root fibers of the 5th nerve.

In 4 patients seen during their attacks of migraine we have injected the stellate and first and second thoracic sympathetic ganglia with novocain. One patient was not relieved; in another the headache stopped with the introduction of the needles before injection and the other 2 had their attacks stopped for the duration of the novocain block. One of the latter has reported 80 to 90 per cent improvement in the subsequent attacks although she had only a novocain injection.

*Eighth Nerve Neuralgia (Ménière's Disease).* A cure for true Ménière's disease by intracranial division of the affected 8th nerve was reported by Dandy<sup>9</sup> in 1928. At that time 9 cases had been relieved from 3 months to 3½ years. A subsequent article<sup>10</sup> reported 30 cases (some having been observed 6 years after operation) in whom there had not been a single attack resembling Ménière's disease subsequent to operation. Coleman and Lyerly<sup>11</sup> and a recent case of ours have substantiated the results of Dandy.

That Ménière's disease is a true neuralgia of the 8th nerve is suggested by the story of a patient "who is perfectly well in every respect, suddenly, without warning and without apparent cause, is seized with a terrific dizzy spell, lasting for several minutes, sometimes hours or even days. The dizzy spell passes off and the patient again is perfectly normal until at a later time a similar attack develops, and again without warning. From that time on life is a succession of just such attacks. Associated with the attacks there is usually vomiting and frequently nausea. Always there is tinnitus and subtotal deafness in one and the same ear." Dandy also describes pseudo-Ménière's disease where the attacks are exactly like those of Ménière's disease but there is never unilateral deafness. Only in true Ménière's disease has section of an already impaired nerve given complete and permanent relief.

*So-called Genuiculate Ganglion Neuralgia.* Ramsay Hunt's neuralgia is of rare occurrence. From observation of patients with Bell's palsy and herpetic vesicles on and in the ear Ramsay Hunt described a neuralgia or otalgia characterized by sharply localized pain in the ear and mastoid region which he felt was due to irritation of the sensory filaments of the 7th nerve, that is, a neuralgia of the nervus intermedius or nerve of Wrisberg and the geniculate ganglion. Clark and Taylor<sup>12</sup> in 1909 reported the only case of a true tic douloureux of the sensory filaments of the facial nerve cured by physiologic extirpation of the geniculate ganglion. Taylor cut the 7th, the pars intermedia and the upper fasciculus of the 8th nerves intracranially. His patient was a woman, aged 28, who for 2 years



suffered from paroxysmal intermittent pain in front of the left ear and in the depths of the ear on the anterior wall of the external meatus. At times there was a moderate degree of neuralgic pain in all three distributions of the 5th nerve and also in the occipital region. As all eye, ear, throat and general physical examinations were negative, the conclusion arrived at by a number of neurologists was that the lesion was a true tic douloureux of the geniculate system of the facial nerve, and that cutting the nerve of Wrisberg or pars intermedia should cure the condition. Following operation "on the twelfth day the patient sat up in a chair 45 minutes. That evening for 2 hours she suffered severe pain in the left ear, which closely resembled the pains before operation. With that single exception she has never for a moment had anything resembling the old pain." Six years later she was seen by Dr. George Crile who reported that she had remained free of pain.

Following the report of this case of a tic douloureux confined to the ear, a controversy appeared in the literature with Mills<sup>13</sup> and Kidd<sup>14</sup> opposing the teaching that the geniculate ganglion in man sends sensory fibers to the skin of the external ear and external auditory meatus. Mills went so far as to suggest, apparently correctly, that it was the decompression resulting from the operation rather than the section of the nerve that cured Taylor's patient. Kidd agreed that there were cases of herpes auris with complete homolateral facial palsy that corresponded closely in the distribution of the herpetic vesicles with Hunt's "zoster zone of the geniculate" but Mills felt that even these cases could be best explained on the supposition of an involvement of ganglia other than the geniculate.

Clark's and Taylor's report remained in the literature as the only case of true tic douloureux of the ear (geniculate neuralgia) that had been operated upon until our recent report<sup>15</sup> of a similar case which was cured by cutting the 9th nerve intracranially and which was termed tympanic plexus neuralgia.

*Tympanic (Jacobson's) Plexus Neuralgia.* In the fall of 1932 a patient was studied in the various departments of our clinic because of severe left aural pain which was paroxysmal in character and seemed to be situated deep in the external auditory meatus. Her story was practically that of Clark's and Taylor's patient so that all concurred in a diagnosis of Hunt's or geniculate neuralgia or tic douloureux of the 7th nerve. Her history and operative findings are briefly summarized.

Miss R. S., aged 31, American, telephone operator, was referred to the Stanford Clinic by Dr. D. Carson in October, 1932. In 1921 a painful left concha caused her to dispense with the left ear phone for a time. Several months (spring 1932) before the onset of her complaint she had a sensation of drawing and discomfort in the left upper half of her face. Early in August the drawing sensation was quite extensive involving the cheek,

forehead and occipital region. A great pressure seemed to be on the bridge of the nose. At this time she had a coryza and an acute sinusitis. Two days later a sharp stabbing pain struck deeply in her ear, causing her to shriek and drop her work for 5 minutes. A number of paroxysms of stabbing pains appeared at irregular intervals throughout the day. They were all identical in type and location, coming without apparent cause as a momentary stab in the anterior wall of the left external auditory meatus and causing her to shriek and grab the side of her head and ear. These paroxysms continued daily. At times there was itching in the external meatus and a dull aching of the ear. A burning sensation of the left face continued for some time after an attack. Left occipital headaches were frequent. When seen in an attack she suddenly cried out, grabbed her left ear or put her little finger into the auditory canal and rocked back and forth in agony. There was no salivation during attacks.

Because there was swelling and injection of the posterior, superior wall of the external auditory canal which was tender but was not a trigger area for the paroxysms, efforts were made to eradicate any foci of infection. Roentgenograms showed evidence of maxillary and ethmoid disease. Antro-tomy was done, the sphenoids and ethmoids were examined and washed. Teeth were extracted. The attacks of neuralgia continued and a fairly constant pain developed in the left face beneath the eye. The sphenopalatine canal was cocaineized which relieved the pain in the ear and face for an hour. The sphenopalatine ganglion was injected with novocain and she was free from pain for 12 days. When it returned the ganglion was injected with alcohol but relief was secured for only 4 hours. Points of tenderness along the left cervical chain were obtained on pressure causing pain in the ear and dilatation of the left pupil but a novocain block of the left sympathetic chain at C<sub>7</sub>, T<sub>1</sub> and T<sub>2</sub> did not stop the paroxysms, nor did cocaineization of the tonsillar region and base of the tongue.

Trichlorethylene inhalations gave no relief. The tics were becoming more frequent and the patient was forced to stop work the latter part of November.

Roentgenograms of the mastoid regions showed a small double spot of increased density on the left which appeared like calcified debris or a tiny sequestrum, but Dr. R. R. Newell was unwilling to make a diagnosis of any mastoid inflammation from the roentgenograms. The skull and cervical spine were normal. Six weeks after the first examination of the ear the canal was slightly injected and when stroked with cotton showed a relative hyperesthesia. The tympanic membrane was of good color and position. The dull pain in the face continued. Hyperthermic baths increased the severity of the pains, galvanism gave no relief.

During the first week in December the paroxysms were coming every 1 to 3 minutes. Sedatives helped very little and the patient begged for relief. As it seemed a true tic douloureux of the geniculate ganglion and similar to the case of Clark and Taylor, operation was advised and permission given to section the 7th and 8th nerves if necessary in attempting to divide the pars intermedia of the seventh.

Operation was performed on December 10, 1932, under local anesthesia. Dandy's<sup>16</sup> unilateral cerebellar approach was made. The 8th, 9th and 10th nerves were easily identified and separated from each other. The 8th nerve was readily exposed and with the 7th was gently touched and moved. The patient stated she felt pain in her external auditory canal but that it was not the tic pain. The 9th nerve was touched which caused her to shriek and to exclaim that she had the tic pain. Four times the 7th and 8th nerves were gently moved and each time when questioned she stated she had a pain in the auditory canal. Four times the glossopharyngeal nerve was gently touched and each time she shrieked out from the stabbing

paroxysmal pain which was identical with the paroxysms she had had for 4 months. The glossopharyngeal nerve was then cut and the patient fell asleep on the operating table.

Over 11 months have elapsed since operation. Never has she felt any suggestion of her tic pain nor has the pain in the face and occipital region returned. Three weeks after operation she was back at work at the telephone exchange, a happy and calm individual.

The salivary secretions were accurately and simultaneously collected from the parotid and submaxillary glands in this patient and in 2 other patients in whom the 9th nerve had been sectioned intracranially. Contrary to the accepted teachings we<sup>17</sup> found that there was an immediate and marked diminution in the secretion of these glands on the side operated upon which, however, approached that of the normal side by the 3rd postoperative month. Collection of salivary secretions of other patients with facial palsy and normal or absent taste and still others, through the courtesy of the otolaryngological department, with avulsed chorda tympani just distal to the facial canal after a radical mastoidectomy, indicated<sup>18</sup> that the secretory fibers to the salivary glands came from the 7th and 9th nerves and that those from the 9th nerve apparently did not course through its tympanic branch but passed peripherally by its auricular anastomotic branch to the facial, in which nerve, by going cephalad, they entered the chorda tympani. From the chorda tympani the fibers to the parotid gland joined the auriculotemporal branch of the 5th, and those to the sublingual and submaxillary joined the lingual branch of the 5th.

Thus a typical so-called geniculate ganglion tic douloureux was cured by intracranial section of the glossopharyngeal nerve.<sup>15</sup> The operation was performed under local anesthesia with the expectation that the pars intermedia of the 7th nerve was at fault and its section contemplated. Fortunately with the patient awake she correctly indicated the nerve involved and insured the successful result.

Following this astonishing revelation that a so-called geniculate neuralgia was really a glossopharyngeal neuralgia it was evident that the tympanic or Jacobson's nerve branch of the glossopharyngeal must have been the only portion of the nerve involved, and one might call it a tic douloureux of Jacobson's nerve or tympanic nerve neuralgia. In Harris'<sup>20</sup> book several case histories are classified under geniculate neuralgia which might properly be placed with partial or tympanic plexus neuralgia of the 9th nerve.

*The Neuralgias of the Glossopharyngeal Nerve.* Two types of neuralgia of the 9th nerve have been described,<sup>15</sup> the partial or tympanic plexus tic douloureux and the complete glossopharyngeal tic douloureux.

The ordinary complete glossopharyngeal neuralgia has only recently been recognized and is still being confused with tic doulou-

reux of the 5th nerve, or else is diagnosed hysteria or psychoneurosis. These poor sufferers have their teeth and tonsils removed, their sinuses and ears treated and their 5th nerve injected or avulsed with no relief from the stabbing lancinating pain, which usually starts in the tonsillar region or base of the tongue and frequently radiates deeply into the ear. Eating, chewing, swallowing or talking or other movements of the tongue or pharynx induce the attacks and frequently a trigger zone is found in the tonsillar fossa or on the lateral side of the base of the tongue. Saliva drools from the mouth during attacks. Occasionally certain areas on the ear are sensitive and when touched may induce an attack. The mouth and pharynx appear normal and the diagnosis is dependent on the characteristic history and the fact that cocaineization (10 per cent) of the tonsillar region and base of tongue will stop the attacks immediately. As reported recently in 3 cases,<sup>19</sup> permanent relief is secured by intracranial section of the 9th nerve, which produces no physical handicap, since the resulting unilateral numbness of the nasopharynx, from Eustachian tube to epiglottis, of the soft palate, posterior pharyngeal wall and tonsillar region, and the loss of taste and sensation over the unilateral posterior third of the tongue, are not noticeable to the patient except by clinical test.

When the patients with glossopharyngeal tic douloureux are operated upon under local anesthesia, their paroxysmal pains in the tonsillar region, the base of the tongue and deep in the ear are reproduced on moving or touching the 9th nerve. Fay<sup>3</sup> has recently described pain in these regions on faradic stimulation of the hypoglossal nerve. Also stimulation or traction on the vagal stump in another case gave direct reference of pain into the tongue, pharynx and ear, suggesting that the hypoglossal nerve carries pain fibers, which it receives extracranially directly from the vagus.

Whether this pain of vagal origin was similar or not to the paroxysmal type of pain that our 3 patients with complete glossopharyngeal neuralgia had is difficult to say. Our first patient with a trigger zone in the tonsillar fossa and a sensitive tragus, movement of which would induce pain, was operated upon under local anesthesia. The 9th nerve was close to the 10th and in freeing it from the upper fibers of the vagus the pulse slowed and subsequently, for a time, he had difficulty in swallowing large boluses of food and a slight weakness of the soft palate attributed to temporary injury to the 10th nerve; yet it was only when the 9th nerve was touched that his pain was reproduced. Likewise the case of tympanic plexus neuralgia experienced pain in the external auditory canal in the approximate region as that of the pain when the 7th and 8th nerves were moved; yet the reproduction of the tic pain occurred only when the 9th nerve was manipulated.

Fay<sup>21</sup> described 2 patients with malignant disease of the base of the tongue annoyed by dull aching pain deep in the ear. One patient

was not relieved by section of the trigeminus and glossopharyngeus intraeraniaUy but the other was relieved of the otalgia by peripheral section of the roots of the vagus. Vagal section gave anesthesia of the conehea of the ear and a small area over the mastoid region.

Otalgia, according to Fay's observations, is of vagal origin. However, his patients suffering from malignant disease experienced "dull aching pain deep in the ear," whereas our patient and the one of Clark and Taylor suffered from true tic douloureux of the ear.

**Summary.** Of all the neuralgie pains in the head and face only those of paroxysmal nature can be classified as a true tic douloureux.

True tic douloureux of one, two or all branches of the 5th nerve is well known and is permanently cured by section of the nerve central to the Gasserian ganglion.

True tic douloureux of a branch (tympanie or Jacobson's nerve) of the 9th nerve has just been described. It has heretofore been considered as a geniculate ganglion neuralgia or tic douloureux of the sensory filaments of the 7th nerve.

True tic douloureux of all the branches of the 9th nerve (glossopharyngeal neuralgia) is being recognized more frequently with over 40 cases reported in the literature. Those in whom the nerve has been sectioned intracranially have been permanently cured.

True tic douloureux of the 8th nerve may be so considered since the paroxysmal character of Ménière's disease is similar to the ties of other nerves. Some 40 cases have remained cured after intracranial section of the 8th nerve.

All of the tics douloureux of the cranial nerves just mentioned, 5th, 8th, and 9th, have been permanently cured by intracranial division of the respective nerves.

Such complete success in treatment has not followed in the case of the other neuralgias of the head and face, such as the atypical or sympathetic facial neuralgia, sphenopalatine or Sluder's neuralgia, vidian neuralgia, migraine and otalgia with facial palsy (Hunt's or geniculate ganglion neuralgia).

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## A SIMPLIFIED APPARATUS FOR DIRECT VENOUS PRESSURE DETERMINATION MODIFIED FROM MORITZ AND V. TABORA.

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IN the office of practically every physician one may find a sphygmomanometer for ascertaining arterial pressure, but in very few offices, in fact in few institutions, is there to be found an apparatus for measurement of venous blood pressure. An accurate determination of this pressure is of almost as much value as that of arterial tension in diagnosis and treatment of cardiovascular disease. In the past, venous pressure was considered of significance only in the diagnosis of congestive heart failure. Recently, however, it has been recognized that venous pressure determinations have a differential diagnostic value in numerous other conditions. In our experience, this has been true in constrictive pericarditis, asthma, chronic pulmonary diseases, abdominal conditions associated with ascites, and obstruction to either vena cava by mediastinitis or tumor. These readings have also been of assistance in determining the necessity for venesection and the response to therapy in cases of congestive heart failure and in evaluating the results of surgery in constrictive pericarditis.

There are, in general, two methods by which venous pressure may be measured: direct and indirect. The indirect method depends upon the external pressure necessary to collapse a vein and, aside from numerous technical objections, necessitates equipment beyond financial reach of many physicians if accurate readings are to be obtained. The direct method is a direct measurement of the pres-

sure within a vein by means of a manometer connected with a needle or cannula introduced into the vessel.

Moritz and v. Tabora, in 1910, described an apparatus and technique for venous pressure determination from which the apparatus described below is modified. The original mechanism was complicated and not well suited for practical clinical use. We shall endeavor to describe an apparatus which every practitioner, no matter how limited his resources, should be able to assemble and use to advantage.

The materials used in the assembly are: a glass tube of even

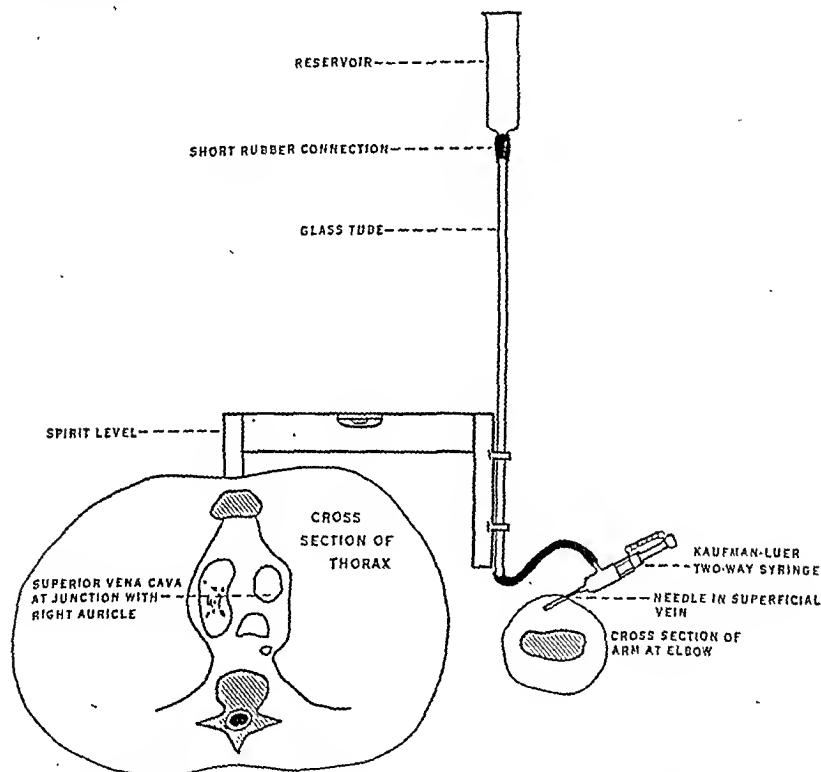


FIG. 1.—Diagram of apparatus in use. The reservoir on top is disconnected when flow into vein is established.

bore, about 35 cm. long (a pipette delivering 1 cc. is very satisfactory), the barrel of an ordinary 10- or 20-cc. syringe, a Kaufman-Luer side arm syringe, a 20-gauge needle of  $1\frac{1}{2}$  inch length, and 2 pieces of rubber tubing (14-F. catheter size), one about 30 cm. long and the other about 4 cm. long. The short piece of rubber tubing is used to connect the reservoir with the top of the glass tubing. The longer rubber piece connects the lower end of the glass tubing and the side arm of the Kaufman-Luer syringe. The needle is placed on the Kaufman-Luer syringe.

Before a venous pressure reading can be made on a patient, the

entire apparatus must be sterilized, which can easily be done in an ordinary sterilizer. The reservoir is filled with sterile physiologic saline solution and then the entire apparatus is filled by lowering the Kaufman-Luer syringe and pulling back its plunger to open the side arm. After precautions are taken to see that no air bubbles are present, the plunger of the two-way syringe is pushed in to the closed position. The apparatus is now ready for venipuncture.

After the patient has been at rest in the supine position, in bed or on a stretcher, for at least 15 minutes, the arm and forearm are extended by the side in supination so that any prominent superficial vein in the cubital fossa is approximately on a level with the right auricle. This, in the average patient, is in a plane about  $2\frac{1}{2}$  inches dorsal to the angle of Louis or, roughly, on a level with the mid-axillary line. A tourniquet is placed on the upper arm to distend the selected vein. After the area to be punctured is prepared with iodine and alcohol, the needle is introduced well into the lumen of the vein. The plunger of the Kaufman-Luer syringe is now withdrawn, allowing the venous blood to enter the proximal  $\frac{1}{2}$  of the syringe barrel. A free back flow of blood indicates that the needle is in the correct position. The tourniquet on the upper arm is now released and as an assistant holds the glass tube and the attached reservoir upright, the Kaufman-Luer syringe plunger is pulled back to open the side arm. The locking chain prevents complete removal of the plunger and serves to hold it steady while a reading is being made. The above maneuvers connect the vertical column of saline directly with the blood stream in the vein lumen. Within reasonable limits (below a pressure in the vein of 350 mm.) the fluid level in the reservoir will begin to fall slowly and the contents of the two-way syringe will begin to clear as the saline enters the vein. As soon as this has occurred the reservoir above is disconnected and put aside. The glass tube is now adjusted so that its lower end, the zero point, is on a level with the needle at its point of entrance into the vein, the tube being held always in a vertical position. The fluid level now falls until the pressure of the column of fluid equals the pressure within the vein.

At this point, in some patients, the height of the fluid column will fluctuate slightly due to changes in the intrathoracic pressure occasioned by the respiratory cycle. In other cases a wave timed with the pulse may be noted. Additional evidence that the fluid column has reached its lowest level is to lower the glass tube a short distance. If the pressure of the fluid column is equal to the venous pressure, the column will immediately rise as the tube is lowered. Conversely, raising the tube will cause the fluid column to drop. At this point, after allowing the column to come back to its original position of equilibrium, we always have the patient increase his intrathoracic pressure by forced efforts at expiration with his glottis closed—i. e., the Valsalva experiment. This will cause a rise in the



height of the fluid column if the system is patent. The patient is now allowed to breathe as before and the column falls to its previous level. The height of the fluid column is now measured by means of a ruler or a steel tape. This measurement, with certain minor corrections to be described below, is the venous pressure. If one obtains a glass tube calibrated in millimeters, or a millimeter scale which may be attached to a plain glass tube, this bother of measuring with a ruler or steel tape is obviated.

Because of the necessarily small lumen of the needle and tubes used in these determinations, a factor of error is introduced by the capillarity. It therefore becomes necessary to make a slight correction

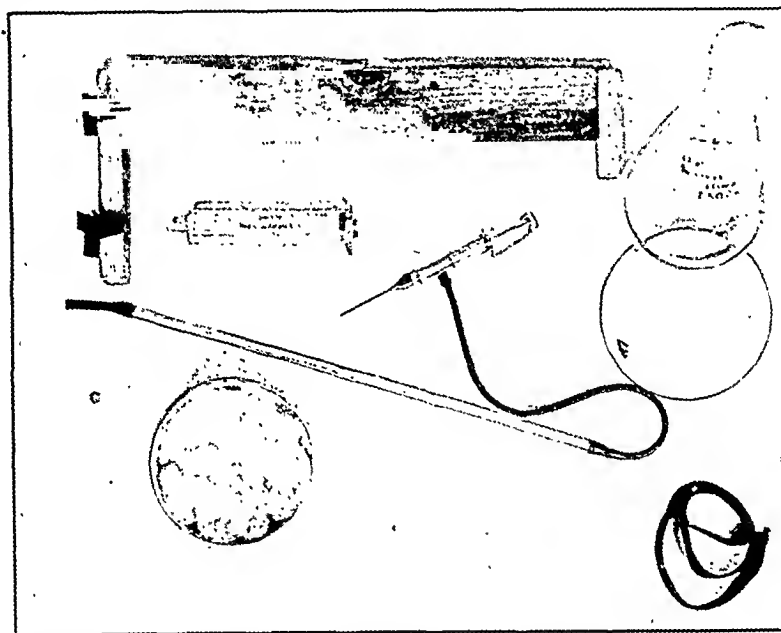


FIG. 2.—Material necessary for determination apparatus, spirit level, alcohol sponges, normal saline and a tourniquet.

in each reading. In order to determine this error due to capillarity, the apparatus is filled with saline as if in preparation for a venous-pressure reading and the needle point immersed in a receptacle containing normal saline. With the lower end of the upright glass tube at the level of the surface of the saline in the receptacle, the system is opened by pulling back the plunger of the two-way syringe. The column of fluid in the glass tube will fall, coming to a standstill somewhere above the zero point. The distance between the top of the fluid column and the zero point measured in mm. is the correction for capillarity and should be subtracted from all the readings made with this particular apparatus. It is most convenient, if a series of determinations on one or more subjects is being made, to employ the same apparatus or duplicates thereof. If, however,

this is impossible, it is most important to calibrate each apparatus for capillarity by the simple method described above.

When indicated, femoral vein readings may be readily and accurately made without any more risk to the patient than arm determinations. The optimal site for venipuncture is a point located at the proximal end of the femoral trigone, about 1 inch distal to the inguinal ligament and just mesial to the point of maximal pulsation of the artery. A tourniquet, of course, cannot be used and is not needed. The zero point of the glass tube is held in the plane of the midaxillary line, provided the patient is on a firm stretcher and not in a sagging bed. The technique is otherwise just as described for venipuncture in the arm veins. It might be helpful to state that we have found the femoral vein located from  $\frac{1}{2}$  to  $1\frac{1}{2}$  inches below the surface and often the needle must be introduced at an angle and to its fullest extent before the vein is reached.

During the course of repeated examinations, we soon discovered that it was difficult to place the arm in the correct position and that this frequently caused erroneous determinations and inaccurate technique. We were able to eliminate this by devising a very convenient, but not absolutely essential, addition to the assembled apparatus, namely, a spirit level with accurately measured uprights on each end. The uprights are so constructed that one is  $2\frac{1}{2}$  inches longer than the other. The shorter upright is allowed to rest on the anterior chest wall at the level of the second costosternal junction (Louis' angle). The glass tube is held in place against the longer upright by two clamps which allow its ready release for cleaning and sterilization. With this addition to the apparatus the level of the vein to be punctured does not have to be taken so accurately into consideration, provided two conditions are fulfilled: first, that the patient be supine with the arm extended by the side; and second, that the lowermost or zero point of the glass tubing is at the lowest edge of the longest upright when the spirit level is horizontal. In different sized thoraces, adjustment should be made, by sliding the tube in the clamps, so that the zero point of the tube is opposite the midaxillary line, which is recognized as approximately the level of the superior vena cava.

In extremely decompensated patients, who are unable to assume the supine position, readings should be made with the arm raised and the zero point of the tube at the level of the second costochondral junction, the patient being as close to supine as possible.

Finally, we feel that we should stress the importance of the following small details: (1) Snugly fitting connections to guard against leakage. (2) Rubber tubing free of old blood clots and air bubbles, to insure an open system. (3) Clean, sharp needles for accurate and relatively painless venipuncture.

Venous pressure has even a wider range of normal than arterial pressure. In a series of 250 readings with this instrument, we have

found a normal range of from 60 to 120 mm. of saline, with the average normal varying from 80 to 110. Any reading above 140 or below 40 should be considered definitely pathologic. Because of the possibilities of error in these determinations, two or more readings, which check reasonably, should be taken on each case studied.

**Summary.** A simple and inexpensive apparatus for venous pressure determination by the direct method of Moritz and v. Tabora is described, together with the technique for its use.

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### FACTS ON DISEASE OF THE CORONARY ARTERIES, BASED ON A SURVEY OF THE CLINICAL AND PATHOLOGIC RECORDS OF 762 CASES.\*

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VALUABLE information concerning the morbidity and mortality from disease is obtained by analysis of clinical records and death certificates. But the facts are apparent only when the check of postmortem examination is critically applied. The increasing death rate from cardiovascular disorders has fired the imagination of the laity and aroused concern in the minds of those whose function it is to conserve the public health. Coronary artery disease, due perhaps in part to the dramatic features of acute obstruction and the frequency with which it terminates the careers of prominent citizens by sudden death, has stimulated an unusual amount of general interest. Certainly during the past two decades, disturbances in the coronary circulation have been subjected to intensive investigation, both in the laboratory and the clinic.

\* Read before the American Climatological and Clinical Association, Washington, D. C., May 9, 1933.

In the files of the Presbyterian Hospital, during the period covered by the years 1910 to 1931 inclusive, 762 autopsy records were found in which affections of the coronary arteries were described. This particular span of years was chosen because the records kept during this time were adequately complete and sufficiently uniform for comparison. During this period, 126,445 patients were admitted to the hospital and 2877 autopsies were performed. Based upon a correlation of the clinical and pathologic data, a series of studies has been made. It is realized that this relatively small number of cases represents only a section of the population residing in a particular eastern American city and that, in view of such limitations with respect to the material, no general conclusions may be drawn. On the other hand the observations, both at the bedside and at the postmortem table, were made with reasonable care. And there is available in the records of the New York City Department of Health an ample background of general statistical information.\* In this paper are presented some of the results of a statistical survey of our cases of coronary artery disease.† More detailed discussion of various aspects of this group of cases will appear in subsequent communications.

*The Material Studied and the Manner of its Collection.* It was apparent as the result of a preliminary study<sup>1</sup> that all cases showing pathologic changes in the coronary vessels were not indexed under coronary headings in the record files of the Department of Pathology. In the earlier years covered by the period under consideration, failure to file such data was due chiefly to lack of interest on the part of the person performing the autopsy; for adequate descriptions were given in the protocols. Even in later years, minor grades of atheroma, in the form of a few intimal plaques, were likewise not noted in the final anatomical diagnoses, perhaps because such changes were relatively common and were not regarded as significant. Indeed, at a given age, what character or extent of change in the arterial wall should be regarded as within the range of normal? At present, there exist no adequate criteria which make possible an answer to this query. In assembling our cases, the point of view was taken that the presence of any lesion signified a deviation from the normal and hence should be considered as pathologic.

In the endeavor to include, as nearly as possible, all of the cases in the autopsy files, each protocol indexed under the following headings was carefully examined: arteriosclerosis of the coronary arteries, thrombosis of a coronary artery, infarct of the myocardium,

\* To Dr. Charles F. Bolduan, Director of Health Education of the New York City Health Department, we are grateful for placing at our disposal the records of this Department.

† We are indebted to Dr. Louis I. Dublin, Statistician and Vice-President of the Metropolitan Life Insurance Company, for helpful criticism with regard to the technique of statistical analysis; and to Mr. Goldstein of his Department, for tabulating the material.

aneurysm of the heart, fibrosis of the myocardium, embolism of a coronary artery, occlusion of the coronary arteries, syphilis of the aorta, stenosis of the orifice of a coronary artery, periarteritis nodosa, rheumatic coronary arteritis and generalized arteriosclerosis. Particularly under this last caption were found numerous cases showing the lesser grades of coronary sclerosis and not included in the diagnostic files as coronary disease.

For estimating the frequency with which the clinical diagnosis of coronary disease was made, only those records were included in which specific diagnostic mention was made of coronary lesions. Thus, cases filed merely as "syphilis of the aorta" or "generalized arteriosclerosis," without reference to coronary involvement, were discarded. In this group obviously there appear a number of fatal cases in which an autopsy was not performed, and others that did not die while under observation.

**DISCUSSION. Etiologic Types.** It is apparent in Table 1, that arteriosclerosis was by far the most common lesion of the coronary arteries, having been found in 97.2 per cent of the cases. Infarction of the myocardium took place not infrequently in the absence of thrombosis. In 13 per cent of the infarcts, aneurysm of the ventricles developed. Syphilitic aortitis, by inducing stenosis or occlusion of the coronary orifices, was responsible for impairing the blood supply of the heart in 5.7 per cent of the total cases. In over one-quarter of the syphilitic group, the heart muscle was the seat of infarction. Coronary embolism was rare, occurring but six times in 2877 autopsies. Periarteritis nodosa involving the coronary vessels, was observed only 3 times and rheumatic coronary arteritis but twice.

TABLE 1.—ETIOLOGIC TYPES OF CORONARY DISEASE AND ASSOCIATED PATHOLOGIC STATES, IN 762 AUTOPSIES ON CASES WITH CORONARY DISEASE, 1910-1931.

Arteriosclerosis . . . . .	742 (97.2%)
Slight . . . . .	157
Moderate . . . . .	220
Calcification, } . . . . .	293
Stenosis or } . . . . .	
Occlusion } . . . . .	72
Thrombosis . . . . .	
Infarct of heart . . . . .	93
Aneurysm of heart . . . . .	12
Rupture of heart . . . . .	3
Syphilis of aorta . . . . .	44 (5.7%)
Stenosis or occlusion of coronary orifice . . . . .	44
Infarct of heart . . . . .	12
Coronary embolism . . . . .	6
Periarteritis nodosa (coronary periarteritis) . . . . .	3
Rheumatic fever (coronary arteritis) . . . . .	2
Coronary compression by amyloid deposits . . . . .	1
Coronary compression by aortic aneurysm . . . . .	1

It has been claimed, notably by Warthin,<sup>2</sup> that syphilis predisposes to the production of coronary sclerosis with its attendant pathology. The figures shown in Table 2 do not substantiate this

assertion, for in this group of cases syphilis was found at autopsy in but 13.4 per cent. This is approximately the incidence of syphilis in the general population of our hospital. As might be anticipated in a series in which 44 cases of luetic aortitis have been deliberately chosen for inclusion, it was in the younger patients that the incidence of syphilis was highest. The close agreement between the Wassermann reaction and the finding of syphilitic lesions at autopsy is noteworthy. In a series of 44 autopsies on cases of coronary disease, Klotz and Lloyd<sup>3</sup> were likewise unable to demonstrate a relation between syphilis and coronary sclerosis. They found evidences of syphilis in 11 per cent—a figure closely approaching ours. Syphilis, then, is present no more frequently in patients with coronary disease than in those without it.

TABLE 2.—INCIDENCE OF SYPHILIS, BY AGE GROUPS, IN 746 AUTOPSIES ON CASES WITH CORONARY DISEASE, 1910-1931.

	No. of cases.*				Per cent of total cases.			
	Total	25-44	45-64	65 and over	Total	25-44	45-64	65 and over
Total autopsies . . .	746	133	408	194	100.0	100.0	100.0	100.0
Syphilis found . . .	100	31	57	11	13.4	23.3	14.0	5.7
Total number tested by Wassermann . . .	555	116	307	123	100.0	100.0	100.0	100.0
Positive Wassermann . . .	82	24	53	4	14.8	20.7	17.3	3.3

\* Age group "0-24" has been omitted because it comprised only 11 cases.

*Incidence.* For purposes of discussion, the interval covered by the years 1910 to 1931 has been divided into two time periods, namely, 1910 to 1919, and 1920 to 1931. In this way, the validity of any changes occurring during these 22 years is enhanced, in that the number of cases involved in the comparison is greater than if subdivision were made into annual periods.

TABLE 3.—COMPARISON BETWEEN CLINICAL AND AUTOPSY INCIDENCE OF CORONARY DIAGNOSES, BY TIME PERIODS, 1910-1931.

Period.	Total hospital admissions.	Clinical coronary diagnoses.	Total autopsies.	Autopsy coronary diagnoses.	Per cent clinical coronary diagnoses of total admissions.	Per cent autopsy coronary diagnoses of total autopsies.
1910-1919	40,682	7	1020	182	. .	17.8
1920-1931	85,963	454	1857	564	.5	30.4
Total	126,645	461	2877	746	.4	25.9

During the second period, due to enlarged facilities in a new building, both the total number of hospital admissions and the total number of autopsies were greater than in the preceding 10 years (Table 3). As diagnosed clinically, the coronary cases comprised but a fraction of a per cent of the total number of hospital patients.

Yet 25.9 per cent of all cases which came to the autopsy table showed lesions of the coronary vessels. This figure corresponds closely to the incidence of significant degrees of coronary sclerosis in a series of 5060 consecutive, routine postmortem examinations at The Mayo Clinic, namely 28.2 per cent.<sup>4</sup> In Glasgow, in a series of 1000 consecutive autopsies, the incidence of coronary disease was even greater; 37.1 per cent of the cases showed a lesion, trifling or severe, by naked-eye observation.<sup>5</sup> The figures are strikingly high.

*The Degree of Coronary Sclerosis by Age Groups.* Affections of the coronaries due to those degenerative changes commonly called arteriosclerotic, were subdivided, quite arbitrarily, into four groups: (1) slight sclerosis, in which an occasional patch of intimal atheroma was present; (2) moderate sclerosis, in which such changes were more extensive; (3) calcification, stenosis or occlusion (the latter non-thrombotic); (4) thrombosis. The vascular lesions in the first group and in many of those in the second were of no functional importance in that they did not impair the nutrition of the heart muscle; and these two groups comprise 50 per cent of the total. Yet even the smallest plaque may assume vital significance if the integrity of the intima is impaired and thrombosis is initiated.

As might be expected, the lesser degrees of sclerosis were observed predominantly in the younger age groups; the more marked lesions developed with advancing years. Thrombosis, on the other hand, occurred with equal frequency during the age periods 25 to 44 and 45 to 64, and declined sharply after age 65 (Table 4).

TABLE 4.—DEGREE OF CORONARY SCLEROSIS, BY AGE GROUPS, IN 746 AUTOPSIES ON CASES WITH CORONARY DISEASE, 1910-1931.

	No. of cases.*				Per cent of total cases.			
	Total	25-44	45-64	65 and over	Total	25-44	45-64	65 and over
Total number rated . . . . .	746	133	408	194	100.0	100.0	100.0	100.0
None† . . . . .	4	2	2	..	.5	1.5	.5	
Slight . . . . .	157	41	84	30	21.0	30.8	20.6	15.5
Moderate . . . . .	220	44	124	49	29.5	33.1	30.4	25.3
Calcification, stenosis or occlusion . . . . .	293	31	157	103	39.3	23.3	38.5	53.1
Thrombosis . . . . .	72	15	41	12	9.7	11.3	10.0	6.2

\* Age group "0-24" has been omitted because it comprised only 11 cases.

† Of these, 2 were cases showing rheumatic coronary arteritis; 1 was an instance of coronary compression by amyloid deposits; another, compression by an aortic aneurysm.

*The Clinical Diagnosis.* From 1910 to 1919, the diagnosis of coronary disease was made but 7 times in 40,682 hospital admissions. In 1919, J. B. Herriek published his second paper on thrombosis of the coronary arteries.<sup>6</sup> It is, perhaps, more than coincidental that during the year 1920, the diagnosis of coronary disease was

made 11 times. From then on, the trend of the incidence of coronary diagnosis was steadily upward, so that in 1931, 8 patients in every 1000 admitted were regarded as having impairment of the cardiac circulation (Fig. 1).

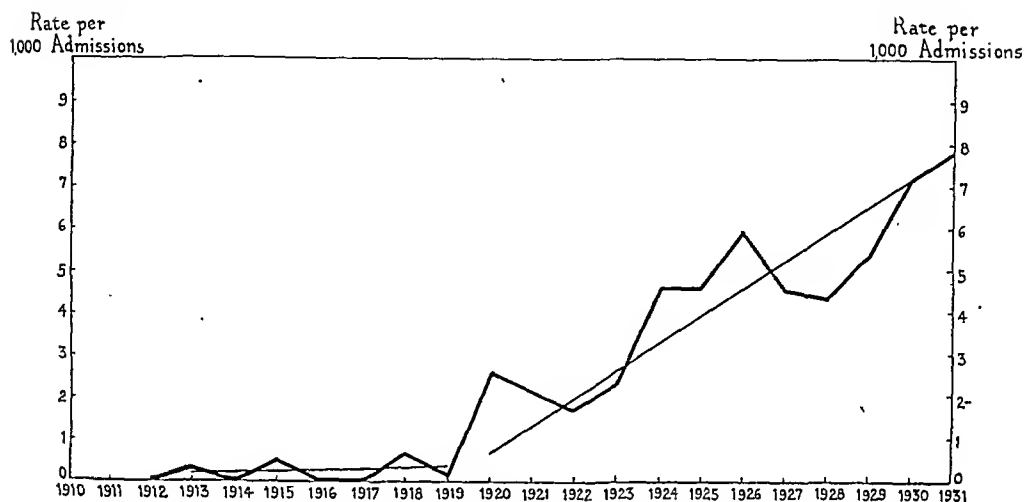


FIG. 1.—Clinical diagnosis of coronary disease per 1000 hospital admissions, 1910-1931.

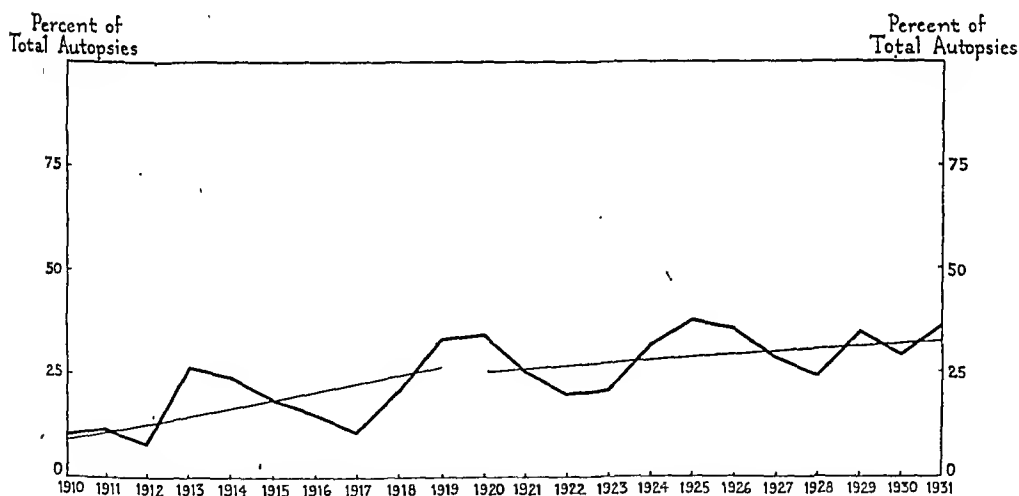


FIG. 2.—Per cent of total autopsies showing coronary disease, 1910-1931.

*The Pathologic Diagnosis.* On the basis of clinical diagnosis alone, it would appear that during the period under consideration there has been a considerable increase in the incidence of coronary disease. But the autopsy figures do not lend support to this idea (Fig. 2). To be sure, throughout the 22 years, the trend is gently but steadily upward. But the sharp discrepancy between the slope of this curve and the one shown in Fig. 1 is striking.

*The Increasing Incidence of Coronary Disease.* In this series of



autopsies, then, as time went on, the incidence of coronary disease actually increased. But the increase was not nearly so great in the proven cases as was indicated by the figures based on clinical diagnosis alone. There are several reasons in explanation of these facts:

1. In New York City, during the period 1910 to 1931, the general death rate has steadily fallen; the lowering of rate obtains at all ages. This decline in death rate has been due almost entirely to effective control of all of the important infectious diseases (Table 5).<sup>\*</sup> Fewer people succumb to infections; but they escape only to die, at a riper age, of degenerative diseases.<sup>7</sup>

TABLE 5.—DEATH RATES PER 100,000 POPULATION, NEW YORK CITY, 1910, 1920 AND 1931.

	1910	1920	1931
Total death rate . . . . .	1604	1289	1092
Pulmonary tuberculosis . . . . .	181.64	108.47	61.64
Other tuberculosis . . . . .	28.88	17.07	7.79
Pneumonias . . . . .	219.83	176.96	130.39
Typhoid fever . . . . .	11.66	2.41	1.09
Diphtheria . . . . .	35.84	18.39	2.62
Scarlet fever . . . . .	19.91	3.87	1.18
Cancer . . . . .	77.53	93.53	117.57
Diabetes . . . . .	16.05	18.91	27.09
Circulatory system diseases . . . . .	220.08	267.34	331.27
Apoplexy . . . . .	19.83	12.63	9.62
Bright's disease and nephritis . . . . .	117.80	85.03	39.58

2. The population of the city during this same period consequently has "aged"—that is, there has been a progressive increase in the percentage of the population aged 35 and over (Table 6). Those in the later decades of life are more likely to suffer from the circulatory disorders associated with arteriosclerosis.

TABLE 6.—THE AGING POPULATION OF NEW YORK CITY. PERCENTAGE COMPOSITION, BY AGE GROUPS 1910, 1920 AND 1930.

	1910	1920	1930
Under 15 . . . . .	28.7	28.4	24.4
15 to 34 . . . . .	40.2	37.2	38.0
35 to 64 . . . . .	28.3	31.3	33.8
65 and over . . . . .	2.84	3.11	3.83

3. There has been a change in fashion with regard to diagnostic terminology. The death rates from apoplexy, Bright's disease and nephritis, and senility have fallen off sharply. Cases formerly so designated have come to be included under the term "Circulatory System Diseases," and so have added to the numbers of the latter group<sup>8</sup> (see also Table 5).

4. Diagnosis is made with greater accuracy. As has been said on another occasion, physicians have become not only "heart-minded" but "coronary conscious."<sup>11</sup> Coronary thrombosis is now rarely called acute indigestion. It is a familiar fact that non-valvular heart disease—the "chronic myocarditis" of the older writers—

<sup>\*</sup> The death rates for cancer and diabetes have risen; the reasons concerned are not pertinent to the present discussion.

is often associated with coronary sclerosis. Many of the milder, non-fatal and atypical forms of coronary disease are being recognized with increasing frequency.

In short, during the 22 years under consideration, there has been, in the autopsied cases, a slight but real and progressive increase in the incidence of affections of the coronary arteries. This may be explained chiefly by the decline of infectious diseases and the aging of the population. The much greater rise in the frequency of the clinical diagnosis of coronary disease is due in large measure to altered fashions in terminology and to sharpened clinical acumen. This state of affairs is not to be deplored or regarded as a matter of concern. Rather should it be a source of satisfaction that, due largely to effective control of infectious diseases, men may survive to an age when disorders incident to senescence carry them off. The prevention of vascular degeneration presents a problem as yet unsolved.

*The Incidence According to Age and Sex.* Coronary artery disease increased at all ages (Fig. 3). The increase is particularly noteworthy between the ages 25 and 44. There is a predominance of males (Fig. 4). In both sexes the number of cases in the later time period has become greater. In the women in this series, the incidence more than doubled.

*The Incidence in Relation to Occupation.* Those who emphasize the rôle of the strain of 20th century existence in causing coronary disease, call attention to the numbers of business executives with great responsibilities who succumb to its ravages. Our figures do not lend support to this point of view (Table 7). The largest percentage of coronary cases was found among foremen and skilled workers, *i. e.*, 44.2 per cent of the total autopsies in this occupational group showed coronary disease. The professional and executive group came second (39 per cent). Next in order of frequency came manual laborers, clerical workers, the semiprofessional and minor executive group, housewives, the retired or unemployed and, finally, the student group. (All of the students were under 25 years of age.) The differences are not great and, in this series at least, occupation has not seemed to play a highly selective part. The high incidence of coronary artery disease in a group of Jewish industrial workers has recently been pointed out,<sup>9</sup> but the observations were not controlled by postmortem examinations.

*The Accuracy of Clinical Diagnosis.* A study of Fig. 5 makes it clear that our clinical acuity has been sharpened. We have become more familiar with the protean manifestations of affections of the coronaries. The cases of slight sclerosis, in which an occasional plaque of intimal atheroma is the only evidence of pathologic change, will probably continue to escape detection when there is no associated functional impairment of the heart. Even where calcification and stenosis were present, the diagnosis was made

during life only in 16 per cent of the cases during the years 1920 to 1931. The figures for coronary thrombosis are especially striking. Thus, in the period 1910 to 1919, only 19 per cent of the cases were recognized at the bedside; in the period 1920 to 1931, 43 per cent were properly designated—an appreciable improvement in the

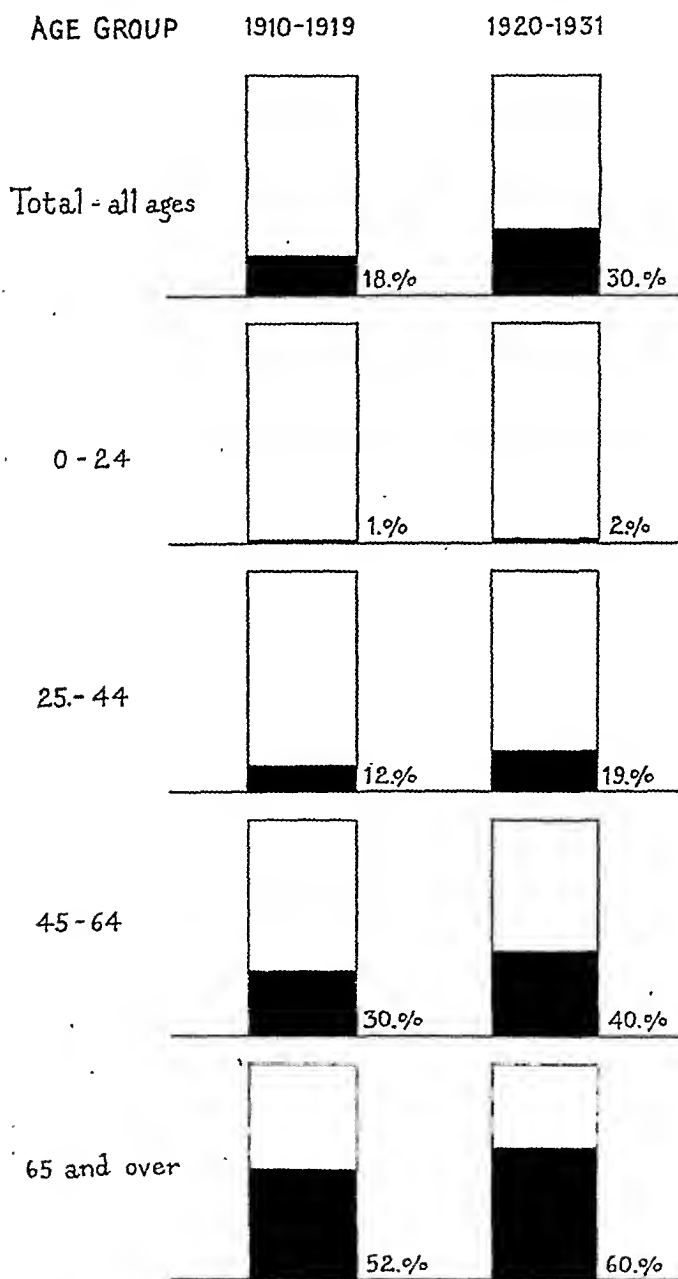


FIG. 3.—Per cent of total autopsies showing coronary disease, by age groups, 1910-1931, in two periods.

accuracy of diagnosis. That so many of these cases escaped detection was due in large part to the great number in which pain was slight or absent. The painless group presents a number of features of interest, and will be made the topic of a separate report.

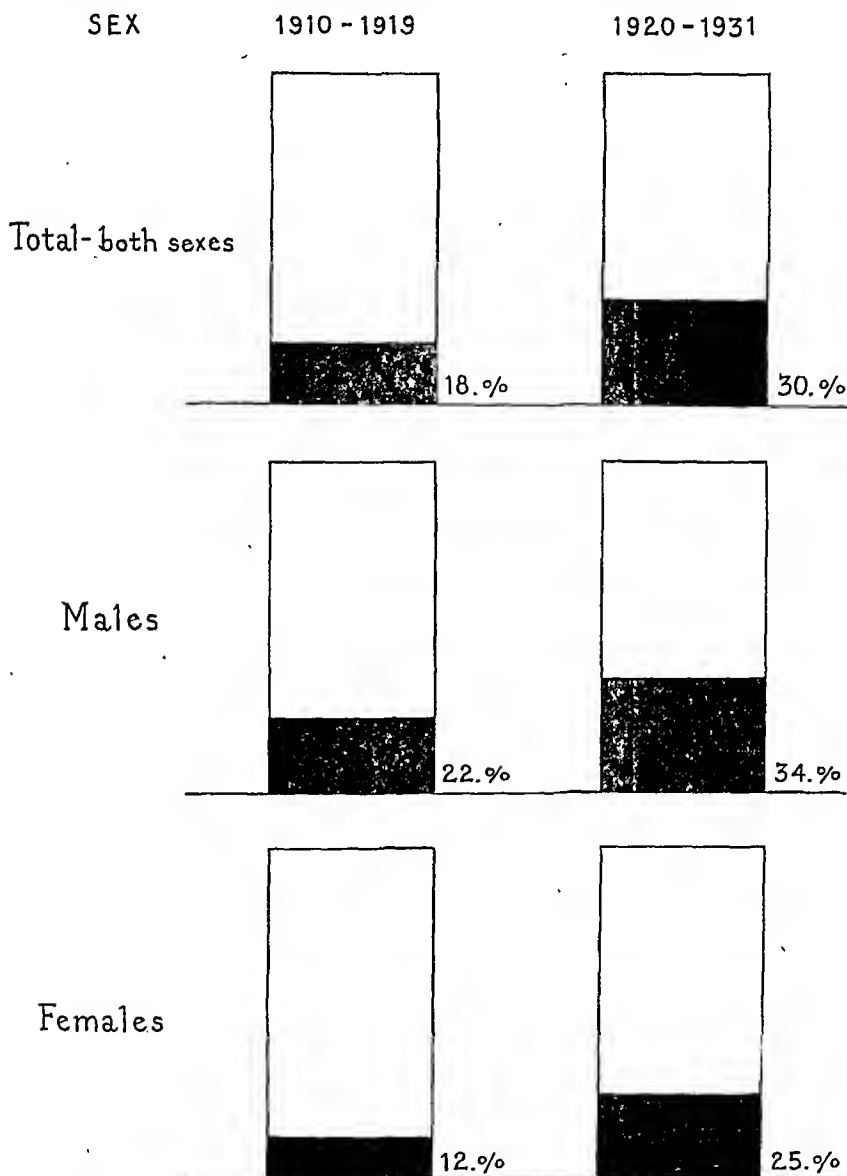


FIG. 4.—Per cent of total autopsies showing coronary disease, by sex, 1910-1931, in two periods.

If so many errors in diagnosis occur in a hospital where every necessary facility is at hand, how much more inaccurate must be the statements in death certificates filled out under less favorable circumstances, and unchecked by postmortem examinations.

TABLE 7.—INCIDENCE OF CORONARY DISEASE IN RELATION TO OCCUPATION IN 762 AUTOPSIES ON CASES WITH CORONARY DISEASE.

Occupational status.	1910-1919			1920-1931			1910-1931		
	Coronary cases.	Total autopsies.	Per cent coronary of total	Coronary cases.	Total autopsies.	Per cent coronary of total.	Coronary cases.	Total autopsies.	Per cent coronary of total.
Infants . . . . .	...	158	0	...	125	0	...	283	0
Housewives . . . . .	24	167	14.4	140	448	31.3	164	615	26.7
Students (under 25) . . . . .	2	52	3.8	2	98	2.0	4	150	2.7
Manual laborers . . . . .	71	317	22.4	66	537	36.7	268	854	31.4
Clerical workers . . . . .	19	81	23.5	50	203	32.5	85	284	30.0
Foremen and skilled workers . . . . .	23	64	36.0	30	101	50.0	73	165	44.2
Semiprofessionals and minor executives . . . . .	8	45	17.8	49	89	33.7	38	134	28.4
Professionals and executives . . . . .	17	49	34.7	30	120	40.8	66	169	39.0
No occupation (retired or unemployed) . . . . .	14	54	26.0	16	113	26.6	44	167	26.4
Not stated . . . . .	4	40	10.0	16	25	64.0	20	65	30.8
Total . . . . .	182	1027	17.7	580	1859	31.2	762	2886	26.4

*The Causes of Death.* Although all of the patients in this series showed pathologic involvement of the coronary arteries, they did not all die of heart disease, nor was this necessarily the condition which induced them to enter the hospital. In the interest of clear-

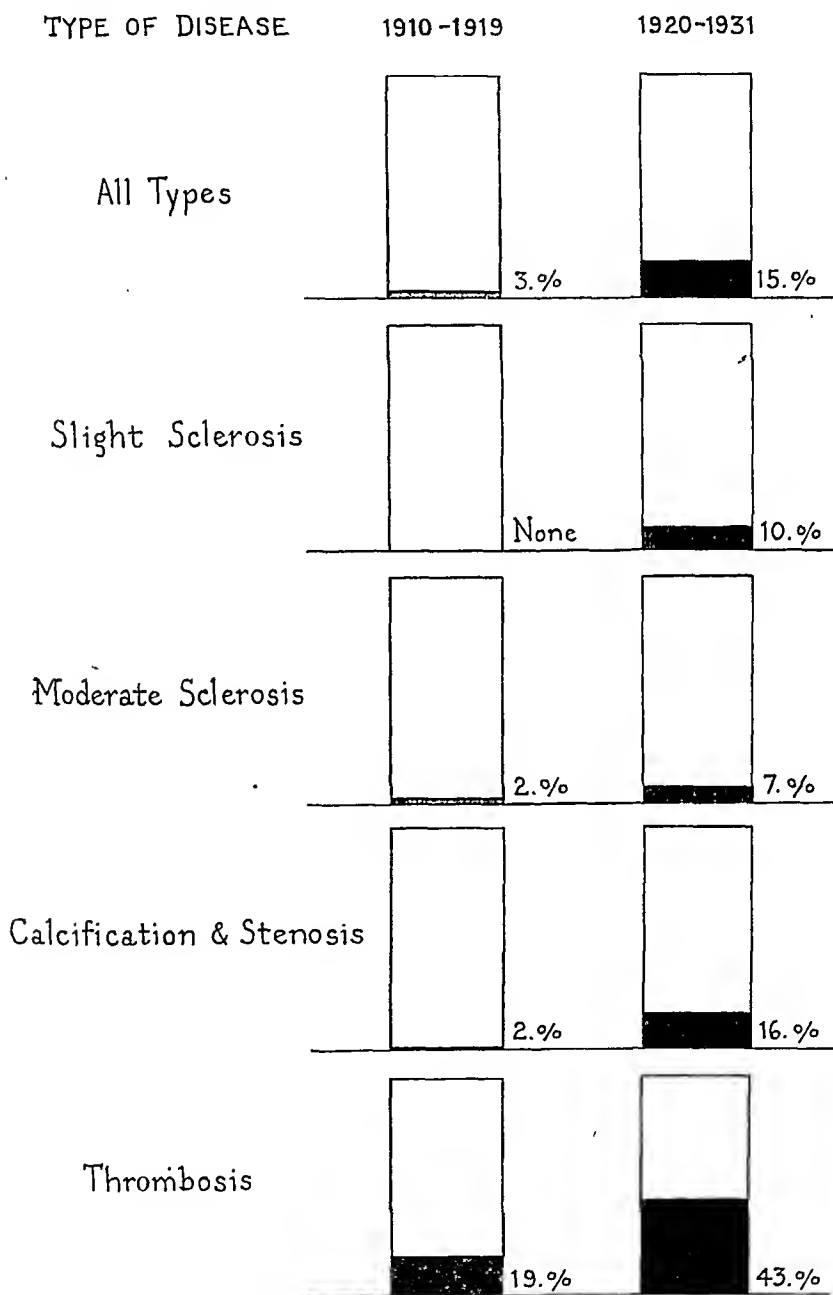


FIG. 5.—Per cent of total autopsies showing coronary disease, recognized clinically, 1910-1931, in two periods.

ness, the causes of death have been divided into "primary" and "secondary."

*Primary Cause of Death.* By this term is meant the disease which may be regarded as the basic pathologic condition. The designations in Table 8 are, for the most part, self-explanatory. Arteriosclerotic cardiovascular disease includes degenerative changes not only in the vessels of the heart but also elsewhere in the arterial tree. A separate group has been made of the cases with arteriosclerosis of the kidneys because they presented a clearly defined clinical picture, which differed sharply from the instances of glomerulonephritis. The latter showed, at autopsy, definite inflammatory changes in the glomeruli.

TABLE 8.—INCIDENCE OF PRIMARY CAUSES OF DEATH, BY AGE GROUPS, IN 746 AUTOPSIES ON CASES WITH CORONARY DISEASE, 1910-1931.

Primary cause of death.	No. of cases.*				Per cent of total cases.			
	Total	25-44	45-64	65 and over	Total	25-44	45-64	65 and over
Total—All causes	746	133	408	194	100.0	100.0	100.0	100.0
Rheumatic heart disease	39	17	16	2	5.2	12.8	3.9	1.0
Arteriosclerotic cardiovascular disease . .	191	18	116	57	25.6	13.5	28.4	29.4
Syphilitic aortitis . .	53	22	29	1	7.1	16.5	7.1	0.5
Pneumonia . . . .	43	6	21	16	5.8	4.5	5.1	8.2
Malignant disease . .	119	7	67	45	16.0	5.3	16.4	23.2
Tuberculosis . . . .	15	1	9	5	2.0	0.8	2.2	2.6
Acute abdominal condition . . . . .	81	9	41	31	10.9	6.8	10.0	16.0
Sepsis . . . . .	30	6	18	5	4.0	4.5	4.4	2.6
Glomerulonephritis . .	40	26	9	2	5.4	19.5	2.2	1.0
Arteriosclerosis of kidneys . . . . .	45	12	28	5	6.0	9.0	6.9	2.6
Hypert thyroidism . .	3	...	3	...	0.4	.....	0.7	
Disease of hematopoietic system . . . .	15	1	7	7	2.0	0.8	1.7	3.6
Diabetes mellitus . . .	22	...	16	6	2.9	.....	3.9	3.1
Trauma . . . . .	2	...	1	1	0.3	.....	0.2	0.5
Disease of liver . . .	10	...	7	3	1.3	.....	1.7	1.5
Other disease . . . .	38	8	20	8	5.1	6.0	4.9	4.1

\* Age group "0-24" has been omitted because it comprised only 11 cases.

Rheumatic heart disease, as might be anticipated, occurred chiefly in the young and caused death in but a small number. Arteriosclerotic cardiovascular disease was the principal primary cause of death (25.6 per cent of the total) and these patients died mainly after 45 years of age. Syphilitic aortitis was the chief lesion in 7.1 per cent, and death occurred, for the most part, between the 25th and 44th years. Malignant disease, occurring, like arteriosclerosis, in later life, was numerically second as the cause of death (16 per cent). Glomerulonephritis carried off chiefly the younger

patients, in contradistinction to arteriosclerosis of the kidneys which caused the death of the more mature. It appears that pathologic change in the coronary arteries may be found as an associated condition in a variety of fatal diseases and over a wide age range.

*Secondary (Immediate) Cause of Death.* This term is used to designate the condition which was directly responsible for the final catastrophe. For example, the primary disease may have been diabetes; the immediate cause of death, sepsis.

In a series of cases selected primarily because they showed lesions in the coronary arteries, it was reasonable to expect that heart failure should be the most frequent terminal event. And so, in Table 9, it appears that, at all ages, cardiac insufficiency led as the immediate cause of death. Sepsis came second, pneumonia third and uremia fourth. In the younger age groups (25 to 44), however, death from renal insufficiency resulting from glomerulonephritis was second only to that from heart failure. In the aged, sepsis and pneumonia more often terminated life.

TABLE 9.—INCIDENCE OF SECONDARY (IMMEDIATE) CAUSES OF DEATH, BY AGE GROUPS, IN 746 AUTOPSIES ON CASES WITH CORONARY DISEASE, 1910-1931.

Secondary (immediate) cause of death.	No. of cases.*				Per cent of total cases.			
	Total	25-44	45-64	65 and over	Total	25-44	45-64	65 and over
Total—All causes	746	133	408	194	100.0	100.0	100.0	100.0
Cardiac insufficiency . . .	314	62	168	80	42.0	46.6	40.7	41.2
Uremia . . . . .	74	29	35	7	9.9	21.8	8.6	3.6
Acidosis (diabetic) . . .	4	...	4	...	0.5	...	1.0	...
Pulmonary embolism . . .	21	2	16	3	2.8	1.5	3.9	1.5
Cerebral embolism . . .	8	...	6	2	1.1	...	1.5	1.0
Cerebral hemorrhage . . .	27	2	19	6	3.6	1.5	4.7	3.1
Pneumonia . . . . .	109	10	55	44	14.6	7.5	13.5	22.7
Sepsis . . . . .	148	21	82	42	19.8	15.7	20.1	21.6
Aneurysm of aorta . . .	11	4	5	2	1.5	3.0	1.2	1.0
Other disease . . . . .	30	3	18	8	4.0	2.2	4.4	4.1

\* Age group "0-24" has been omitted because it comprised only 11 cases.

**Summary.** 1. A statistical analysis was made of the autopsy and clinical records of 762 cases of coronary artery disease observed at the Presbyterian Hospital during the period 1910 to 1931. The facts apparent as a result of this survey are to be regarded as applying to this material; no general conclusions are drawn.

2. Arteriosclerosis was the most common lesion, having been found in 97.2 per cent of the cases. Syphilitic aortitis, by inducing stenosis or occlusion of the coronary orifices, was responsible for impairing the coronary blood flow in 5.7 per cent.

3. Syphilis did not play a rôle in predisposing to coronary sclerosis. It was present no more frequently in patients with coronary disease than in those without it.



4. In 2877 consecutive autopsies, lesions of the coronary arteries were found in 25.9 per cent. This is a strikingly high figure.

5. In half of the cases showing sclerosis in the coronaries, the lesions were "slight" or "moderate;" in many of these instances, no functional impairment of the cardiac circulation was induced by such lesions. The lesser degrees of sclerosis were observed predominantly in the younger age groups; the more marked lesions developed with advancing years.

6. In this series of autopsies, the incidence of coronary disease showed a slight but steady increase throughout a 22-year period; but the increase was not nearly so great in the proven cases as was indicated by the figures based on clinical diagnosis alone. The reasons in explanation of these facts have been given.

7. Coronary artery disease increased at all ages, but the increase was particularly noteworthy between the ages 25 and 44. There was a predominance of males. The number of cases increased in both sexes.

8. Occupation did not appear to play a significant part in determining those whose vessels were affected. The largest percentage of coronary cases was found among foremen and skilled workers.

9. The clinical diagnosis of coronary disease is being made with greater accuracy as well as with increased frequency. Many cases are latent and probably cannot be recognized during life. Even in the presence of calcification or stenosis, the diagnosis was made clinically in but 16 per cent of the cases during the years 1920 to 1931. During this same period, coronary thrombosis was correctly diagnosticated in only 43 per cent of the cases.

10. Arteriosclerotic heart disease was the most frequent primary cause of death. Cardiac insufficiency was the commonest terminal event.

11. The increase in the incidence of affections of the coronary arteries is not to be regarded as a matter of concern. Rather should it be a source of satisfaction that, due largely to effective control of infectious diseases, men may survive to an age when disorders incident to senescence lead to the termination of life.

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## THE DIFFERENTIATION OF ACUTE CORONARY ARTERY THROMBOSIS FROM PULMONARY EMBOLIZATION.

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PULMONARY embolism may be the cause of a syndrome characterized by intrathoracic oppression or pain, dyspnea, cyanosis, shock, and sometimes sudden death. This syndrome closely resembles the clinical picture of acute coronary artery thrombosis. In 1908 Von Neusser<sup>1</sup> in his truly remarkable lectures on angina pectoris commented on the necessity for differentiating "paroxysmal sternocardiac pain" from the syndrome of pulmonary embolization. No further conspicuous discussion of this problem appeared in the literature until a very recent communication by Hamburger and Saphir.<sup>2</sup> They reported 5 cases with autopsies and remarked on the need for a more general recognition of this problem in differential diagnosis.

In the past 3 years we have collected the following 6 cases who were presumed to have had fatal attacks of coronary artery thrombosis but in whom necropsy revealed that they had succumbed to pulmonary embolization. In 2 instances the diagnosis was made particularly difficult by the fact that coronary artery disease had previously been present, and its existence was confirmed by the history, physical and laboratory findings. The fatal episode, on the other hand, was caused by a pulmonary embolus and not by the primary vascular disease of the heart. In the other 4 cases no previous clinical or laboratory evidence of coronary artery disease had been present, but the cause of death ascribed to coronary thrombosis was shown by autopsy to be due to pulmonary embolus.

**Presentation of Cases.** CASE 1.—R. J., a woman, aged 55, was admitted for preeordial pain starting that morning. Six months before, she suddenly experienced agonizing preeordial pain radiating to the left scapular region and accompanied by dyspnea, orthopnea and weakness. There were several recurrences of this syndrome after the first attack. Recently there had been some right lower extremity pain with transient swelling of the limb. Examination revealed an acutely ill elderly female, dyspneic and complaining of chest pain. The lungs were emphysematous and there were some inconstant râles at the right base. The heart was greatly enlarged to both right and left. Heart sounds were poor, but regular. A systolic apical murmur and a loud second aortic sound were present. The liver was enlarged to the umbilicus. There was no ascites. Blood pressure was 135 systolic and 85 diastolic. The blood Wassermann test was negative. The electrocardiogram showed left ventricular preponderance, negative T wave in Lead I, abnormal R-T segments, and widened and high Q-R-S complexes—resembling the record seen in long standing cases of arterial

hypertension. The diagnosis of coronary artery disease with myocardial insufficiency was thereby established.

Under observation the patient became more dyspneic, cyanotic and edematous. The right border of the heart percussed farther out. It was thought by the clinicians that the picture was caused by another coronary thrombosis.

**RELEVANT POSTMORTEM FINDINGS (Dr. W. Kantrowitz).** *Lungs.* The right lower lobe of the lung was the site of a large wedge-shaped hemorrhagic infarct which occupies practically the entire lobe. *The main branch of the pulmonary artery supplying this lobe was occluded by a large recent but adherent embolus.* The lungs were edematous.

*Heart.* Universal cardiac enlargement with adherent pericardium. On the anterior portion of the left ventricle, near the apex, was an old aneurysmal bulging of the wall with calcified margin. *The left anterior descending coronary artery was completely obliterated and calcified (old closure).* The other coronary vessels showed arteriosclerotic changes and narrowing of their lumina but no closures.

*Saphenous Vein.* The left saphenous vein was the site of a long thrombus, the proximal end of which showed a sharp breaking off. The vein proximal to the thrombus was empty.

*Summary.* (1) Coronary sclerosis with old closure and obliteration of left anterior descending artery and aneurysm of left ventricle with calcification; (2) pulmonary embolus with infarct of right lower lobe arising from the thrombosis of the left saphenous vein; (3) adherent pericarditis.

*Comment.* Case 1. With so clear a history of previous attacks of angina pectoris due to coronary artery disease, it was reasonable to interpret the last episode of chest pain as another attack. Both physical examination and electrocardiographic findings supported this diagnosis. Nevertheless, in retrospect, one point now appears worthy of mention which might have been of aid in directing attention to the possibility of a pulmonary embolism. The history of the recent occurrence of pain and swelling in a lower extremity should have suggested the possibility of an embolus from a venous thrombosis on the leg. However, in view of the minimal pulmonary signs, the absence of hemorrhagic sputum, and the inability to have this sick patient Roentgen-rayed, the diagnosis of pulmonary embolism, even if suspected, would have been difficult to prove. This case exemplifies the association in 1 patient of both conditions and the extreme difficulty of their clinical differentiation.

**CASE 2.**—I. T., a clerk, aged 44, was admitted complaining of orthopnea, productive cough and (once) severe substernal pain with radiation down the left arm. He had consulted physicians 6 years before for intermittent claudication and they established the diagnosis of thrombo-angiitis obliterans. Gangrene in one small toe had necessitated amputation. Eight months previous to admission he had had attacks of precordial (not substernal) pain with radiation to the left shoulder and arm and occasionally to the right side. In the attacks initiated by effort and excitement—but also occurring while in bed—the patient was pale, perspiring, quiet, and had a sense of impending death. They lasted from 2 to 4 minutes, and relief was obtained by sublingual medication of nitrites or hypodermic injections of morphin. After the first one he was incapacitated for 12 weeks and thereafter suffered from dyspnea on exertion. About 2 weeks before admission a series of similar attacks recurred.

*Examination* showed a well nourished and well developed man, dyspneic but not cyanotic. The pupils were active and there were some basal pulmonary râles. The heart sounds were of poor quality, the second pulmonic sound was louder than the second aortic and reduplicated. Occasional extra systoles were heard. The liver was soft and extended one finger breadth below the costal margin. The right fifth toe had been amputated; no arterial pulsations were present in either foot. The reflexes were normal. Blood pressure was 130 systolic and 64 diastolic. Urine and Wassermann tests were negative. The electrocardiogram showed the typical picture of an intraventricular conduction defect. It was felt that this patient had coronary artery disease with the syndrome of angina pectoris and that undoubtedly there had occurred some occlusions of small coronary vessels.

During a 10-day hospital stay the patient was free of any chest pain. While getting into bed from a wheel chair he suddenly developed an episode of paroxysmal dyspnea and cyanosis, became comatose and died. Several respirations occurred after the cessation of heart beats. This fatal episode was considered another attack of coronary thrombosis.

**RELEVANT POSTMORTEM FINDINGS** (Dr. L. Lichtenstien). *Lungs.* Scattered over the surfaces of both lungs there were large areas which were bluish-red in color and well demarcated from the adjoining aerated mottled areas. There was a hypercrepitant consistency to the lungs, indicating emphysema. *The pulmonary artery conus and both pulmonary branches contain soft embolic masses, grayish-red in color. They were not adherent. In both pulmonary arteries and in the small branches, particularly near the bifurcation, there were small adherent whitish-pink masses representing old organized emboli. Pulmonary veins were negative.*

*Heart.* The right ventricle was hypertrophied and dilated. On the lower half of the interventricular septum, extending to the apex, was an area of myocardial fibrosis 2 by 3 cm. The left ventricle was somewhat hypertrophied; myocardium was brownish-red in color with yellowish streaks. *The coronary arteries were patent and showed some intimal thickening with some narrowing of the left anterior descending and circumflex branch. No occlusions could be discovered.*

*Summary.* (1) Organized and recent bilateral pulmonary embolisms; (2) moderate sclerosis of left coronary artery with myocardial fibrosis; (3) pulmonary emphysema; (4) phlebitis, right iliac vein (?); (5) status after amputation of right fifth toe for gangrene (Thrombo-angiitis obliterans); (6) healed infarcts of spleen and kidneys; (7) brown induration of lungs.

*Comment.* Case 2. Although it has never been emphasized, the incidence of embolic phenomena in cases of extensive peripheral vascular involvement (arteries and veins) such as occurs in thrombo-angiitis obliterans is probably not uncommon. Coronary artery disease and coronary artery thrombosis are likewise frequent in this disease (Averbuck and Silbert<sup>3</sup>). Unquestionably this patient suffered many attacks of angina pectoris dependent upon coronary sclerosis. The seemingly typical nature of some of the attacks and the electrocardiographic findings gave adequate ground for this diagnosis and at autopsy a fibrotically replaced myocardial area was found. There was no fresh myocardial infarction or coronary artery thrombosis, however, to substantiate the clinical impression of a coronary occlusion. In view of the postmortem findings of fresh and old emboli in the pulmonary artery and branches, the conclusion is warranted that some of the attacks described in the

history were due to pulmonary emboli arising from the thrombotic process in the vessels of the lower extremities. Surely, the last attack—characterized by dyspnea and cyanosis, absence of pain and rapidly ensuing coma—was due to a pulmonary embolus.

Besides indicating a difficult diagnostic problem, this case illustrates that an individual may survive repeated small pulmonary embolizations. When many pulmonary artery branches become plugged additional emboli may prove fatal.

CASE 3.—D. S., a housewife, aged 57, entered the Gynecological Service because of sticking pain in the left upper quadrant and an abdominal mass. Examination, study and biopsy established the diagnosis of adenocarcinoma of the rectum with coincident ovarian and pelvic carcinoma. Blood pressure was 152 systolic and 80 diastolic. Urine and Wassermann tests were negative.

Three days after her admission she awoke from her sleep complaining of precordial pain. She was cyanotic, cold, and terrified, with perspiring clammy skin. The picture resembled shock with the pulse varying in quality to imperceptibility, systolic blood pressure ranging from 90 to 40, respiratory rate 46, and poor heart sounds. The heart appeared to be displaced to the left and bronchial breathing was heard over the right lung. Stimulation and oxygen were administered and the patient recovered somewhat. The precordial pain recurred a few hours later and radiation to the left arm was present at this time. *The clinical picture was explained on a basis of a coronary thrombosis with myocardial infarction.* Electrocardiogram showed the T wave in the third lead slightly inverted and cove shaped, the T waves in Leads I and II upright and coved. After another episode of precordial pain the patient ceased.

RELEVANT AUTOPSY FINDINGS (Dr. E. B. Greenspan). *Lungs.* A large reddish-black embolus filled up the pulmonary artery above the pulmonary cusps. The embolus then was broken and parts of this mass were found to be present in both the right and left pulmonary artery branches. Pulmonary veins are negative.

*Heart.* The coronary arteries showed only slight arteriosclerotic flecking and the remainder of the heart appeared normal for this age. An ulcerating adenocarcinoma arising in the rectum and involving the regional lymph nodes and pelvic organs was present. There was extension of the growth into the inferior vena cava.

*Summary.* (1) Ulcerating adenocarcinoma of rectum with metastases to iliac nodes; (2) tumor extension into the inferior vena cava; (3) embolus in right heart, pulmonary conus and both branches of the pulmonary artery.

*Comment.* Case 3. There had been no operation in this case. The sudden onset of severe and recurring precordial pain with the typical "coronary" radiation, dyspnea, cyanosis, angor animi, and the general appearance of shock, all seemed to justify the diagnosis of a coronary thrombosis. Yet a few features which might have been of aid in the differentiation may be pointed out. Coronary thrombosis is rare in women unless associated with arterial hypertension or diabetes, neither of which was present in this instance. There was no previous history of any cardiac complaints or anginoid attacks. The electrocardiogram taken in the hospital during the last episodes did not show the usual changes seen in coronary artery closure. Aside from the picture of shock, dyspnea and cyanosis

were the outstanding signs. Lastly, there was unmistakable pelvic disease which predisposes to embolic phenomena. Although incapable of substantiation at that time, the diagnosis of pulmonary embolus was at least as likely to be correct as the diagnosis of coronary thrombosis.

CASE 4.—S. F., a woman, aged 70, was admitted with a history that 5 days before admission while walking she experienced sudden substernal pain, without radiation, which caused great weakness and dyspnea. She had to go to bed. A chronic cough which she had had for many years now became painful. Orthopnea and dyspnea, some elevation of the temperature and ankle edema appeared. Hypertension was noted for the first time a day before admission. Examination revealed an acutely ill, obese, dyspneic, cyanotic female. Temperature was 100, pulse, 108, and respirations, 24. She was complaining of substernal pain. In the lungs there were some hypostatic râles at both bases, but no alteration in voice or breath sounds. The heart sounds were distant and poor in quality. The second pulmonic heart sound was louder than the aortic second sound; there were no friction rubs heard. No other noteworthy features appeared in the examination. Blood pressure was 150 systolic and 74 diastolic. Total leukocytes were 16,200, polymorphonuclears, 76 per cent; lymphocytes, 20 per cent; mononuclears, 4 per cent. Small amounts of sugar were present in the urine and the blood sugar was elevated. Blood  $\text{CO}_2$ —38 vol. per cent. The blood Wassermann test was negative. The electrocardiogram showed *T* waves in Leads I and II partly inverted with the *T* wave in Lead III low. The diagnosis was coronary artery thrombosis and diabetes mellitus. A day after her admission the temperature rose quickly to 105° F, the pulse and heart action became poor, the respirations more rapid and labored, and the patient ceased.

RELEVANT AUTOPSY FINDINGS (Dr. E. B. Greenspan). The pulmonary arterial tree showed marked arteriosclerotic changes. *In the trunk of the right pulmonary artery, straddling its bifurcation, was a mass of adherent clots with extensions into several smaller arterial branches.* The heart was moderately enlarged and weighed 500 gm. The myocardium was pale and on cut section showed yellowish streaks of fat penetrating toward the endocardial surface. Small adherent thrombi were present in the auricular appendage and wall of the right ventricle which was distinctly hypertrophied. *The coronary arteries except for occasional yellow flecking showed no gross changes.*

Summary. (1) Embolus of right pulmonary artery and branches; (2) acute purulent bronchitis; (3) atherosclerosis of pulmonary arterial tree; (4) adherent small thrombi in the right auricle and ventricle.

Comment. Case 4. An attack of severe substernal pain in a 70-year-old woman who had diabetes mellitus surely warranted the diagnosis of coronary artery thrombosis. The suggestive electrocardiogram lent support to this diagnosis. In view of the autopsy findings, however, which failed to reveal a closed coronary artery but which showed a large pulmonary artery embolus, the absence of radiation of the pain and *the extreme dyspnea and cyanosis* become significant. Here again one can only learn that where the clinical picture of an assumed acute coronary thrombosis is not typical in most of its features the possibility of pulmonary embolization must be kept in mind, especially if cyanosis and dyspnea are marked and begin suddenly.

CASE 5.—F. K., a woman, aged 59, was admitted with a 3-year history of shortness of breath, and orthopnea. She was known to have had arterial hypertension. Edema of the lower extremities made its first appearance 1 year before. A month previous to admission she had suffered an attack of grippe. She continued to cough after this illness. A few days before her admission to the hospital she suddenly became markedly cyanotic, dyspneic and stuporous. Upon admission she was almost comatose. *Cyanosis and dyspnea were both marked.* The heart was tremendously enlarged, particularly to the left. A systolic apical murmur and gallop rhythm were heard. All the peripheral pulses were present. Blood pressure was 100 systolic and 80 diastolic. There were signs of consolidation along with many râles over the lower left lung lobe. The liver was enlarged 4 finger-breadths below the costal margin, and there was pretibial edema. The condition did not improve in spite of active therapy, although a few hours after admission, the blood pressure rose again to 200 systolic and 110 diastolic. Electrocardiogram showed a tachycardia, left ventricular preponderance, and partial inversion of the *T* wave in Lead I. This state continued until death ensued.

She was considered to be a case of essential hypertension who had suffered a previous coronary closure (1 month ago) and who, before admission, again had sustained a major coronary artery occlusion which caused the fatal termination. The lung signs were interpreted as evidence of a confluent bronchopneumonia.

RELEVANT AUTOPSY FINDINGS (Dr. J. Ehrlich). *Chest.* There was a massive effusion on the left side. The right side was free of adhesions or fluid. The right lung was voluminous, its pleura smooth. There was marked congestion and a large amount of fluid ran off the cut surface on slight pressure. The smaller branches of the pulmonary artery were thickened with raised yellowish intimal patches. The bronchi were congested and contained frothy brownish fluid. The left lung was completely atelectatic and represented by a small shrunken mass less than half the size of the right. The apical portion of the upper lobe was raised and firm and deep red in color. *On section a hemorrhagic, wedge shaped area was seen, the size of a pecan nut. One of the medium sized pulmonary arteries traced from the hilus to this area was occluded for a distance of about 2 cm. by a thrombus which, in its proximal portion, was rounded and hung free in the lumen of the vessel.* The occluded vessel does not present any gross disease of its wall exceeding that seen in the other vessels.

*Heart.* No increase in pericardial fluid. The left side of the heart was of tremendous size, globular in form and exceedingly firm. On opening the ventricles, the right heart was seen to be moderately dilated and hypertrophied. The left side had a small cavity and a wall  $3\frac{1}{2}$  cm. in thickness near the base. The myocardium did not show gross fibrosis or myomalacia.

*The coronary arteries were moderately atherosclerotic, but everywhere patent.* There was atherosclerosis of the aortic and mitral valves and the aorta; the pulmonary valves were negative.

*Summary.* (1) Embolism of medium sized branch of pulmonary artery to left upper lobe; (2) hemorrhagic infarction of upper part of left upper lobe; (3) massive left pleural effusion; (4) marked hypertrophy of left ventricle; (5) coronary sclerosis, aortic and peripheral arteriosclerosis; (6) chronic passive congestion of liver and spleen; (7) early stage of arteriolar nephrocirrhosis.

*Comment.* Case 5. Here again the diagnosis of coronary artery thrombosis was justified in a woman of 59, known to have arterial hypertension. A large majority of patients with essential hypertension who die in cardiac failure have severe sclerosis of the coronary

arteries, frequently with thrombosis. Yet the history does not mention substernal pain, nor were there any previous anginoid attacks. The episode just before her death was characterized by the sudden onset of severe cyanosis and dyspnea, shock and stupor. There were signs of extensive pulmonary infiltration interpreted as signs of a confluent bronchopneumonia. Had the possibility of a pulmonary embolus been considered the points in the history enumerated above, in conjunction with the signs in the lungs, would have been of helpful diagnostic value.

CASE 6.—R. G., a woman, aged 52, was admitted to the Surgical Service in November, 1931. She had had right upper quadrant pain for 19 years and jaundice for 6 weeks, with irregular fever, vomiting and one chill. She was a known diabetic. Examination showed a moderately icteric, obese female, who seemed to be comfortable. The heart and lungs were normal. The abdomen was obese, and the liver could be felt 3 finger-breadths below the costal margin. Slight epigastric tenderness was present. The gall bladder could not be felt. The uterus was prolapsed. The blood pressure was 150 systolic and 88 diastolic. The urinary sugar averaged about 1 per cent. The blood Wassermann test was negative. Diagnoses of cholelithiasis with cholecystitis, stone in the common duct, diabetes mellitus and prolapsus uteri were established. The patient was operated upon under spinal anesthesia supplemented by gas, oxygen and ether and the common duct was emptied of stones and drained. For a week after the operation convalescence proceeded satisfactorily. One afternoon the patient suddenly complained of severe precordial oppression and dyspnea. She became cyanotic and presented the picture of collapse. Because insulin was being administered thrice daily the possibility of insulin shock was considered. A blood sugar test of 120 mg., however, eliminated this possibility. Recovering from this episode, the patient did well for a few days. Five days later there occurred another attack of severe paroxysmal dyspnea, with cyanosis and shock. Pulse 146, respirations 48. In spite of active stimulation the patient went quickly into a coma and died.

RELEVANT AUTOPSY FINDING (Dr. J. Ehrlich). *Lungs.* The right pulmonary artery was filled with a coiled up, firm thrombus which was slightly adherent to the vessel wall and which extended for a short distance. The clot had a fairly uniform diameter of  $\frac{1}{2}$  inch. No older, more adherent emboli were to be found in any of the smaller artery branches. No pulmonary infarctions. Pulmonary veins were normal.

*Heart.* The heart was flabby but not enlarged. Valves and endocardium were normal. In the right ventricle a coiled firm thrombus about 1 cm. in diameter and about 15 cm. in length was found lying free in the right ventricular cavity, situated mainly in the outflow tract. Both coronary arteries were patent and did not show any thrombus or marked arteriosclerotic changes.

*Summary.* (1) Embolism of right pulmonary artery and right ventricle; (2) status after choledochotomy and drainage.

*Comment.* Case 6. In this instance the circumstance of the insulin administration brought another possibility into consideration, that of insulin shock. The normal blood sugar level and the inability of the administration of orange juice to influence the symptoms quickly eliminated this possibility. The difficulty of certainly differentiating pulmonary embolization from a coronary closure



still remained. Of particular significance is the fact that the episodes occurred in an apparently healthy subject, postoperatively.

**Discussion.** The clinical picture of an acute coronary artery thrombosis is difficult to present briefly. The symptoms and signs depend upon the artery involved, the state of the other cardiac arteries and myocardium, and the reaction of the individual affected. Nevertheless, there are certain features which occur commonly. Severe substernal, epigastric or precordial pain which appears suddenly, perhaps radiating to the left or right shoulder, to the neck or to the jaw is frequent. Dyspnea need not be a pronounced symptom; it may be present in moderate degree. In the hyposensitive or in isolated left ventricular failure due to closure of a medium sized artery dyspnea can be severe. Often the breathing is shallow, rapid and restrained. With occlusion of a larger coronary vessel, cyanosis may be slight, patients presenting rather an ashen-gray color. Sweating, coldness of the extremities, a rapid thready pulse, diminished blood pressure, feeble heart sounds complete the general picture of shock. Sudden death is common. Pericardial friction rubs, basal lung râles or pulmonary edema occur.

Pulmonary embolus usually induces a syndrome characterized by the sudden appearance of painful oppression somewhere in the chest *with extreme cyanosis and dyspnea*. The pain has no typical radiation and often is of the type that can perhaps better be described as a strangling sensation, a sense of intrathoracic suffocation which provokes an *angor animi* as profound as that which occurs in *angina pectoris* or coronary thrombosis. In many cases shock accompanies the onset, and death occurs almost immediately. According to Edens<sup>4</sup> these sudden deaths are accounted for by vagal stimulation, the mechanical obstruction being insufficient. In those who survive the original shock, dyspnea and cyanosis, fever, and the appearance of pulmonary râles and abnormal breathing constitute the clinical picture. In other cases the heart fails comparatively rapidly. Increasing cyanosis, quickly enlarging liver, and dilatation of the heart to the right signify the right ventricular failure. Cough with the expectoration of sanguineous sputum, pleural rubs and painful respiration depend upon the branch of the pulmonary artery and the area of lung involved. Recovery is not uncommon.

It is thus obvious how confusion in the diagnosis of these two syndromes might readily result. Accurate diagnosis becomes even more difficult in the frequent atypical forms. For instance, as has been emphasized by Libman,<sup>5</sup> hyposensitive individuals may suffer a coronary artery closure without pain, but demonstrate a severe dyspnea instead. On the other hand pulmonary emboli may cause severe pain in the left side of the chest, or occur without hemoptysis. Such cases as well as those with little cyanosis and dyspnea, because of rapidly ensuing shock, present the most difficult problems in differential diagnosis.

There is little to be gained by an extended discussion of theoretical factors that might aid in distinguishing these two conditions. A review of the clinical histories presented in the light of the autopsy findings suggests some general points which would seem to promise real help if applied to future cases.

When the clinical picture suggesting coronary artery thrombosis occurs in a female patient who has neither arterial hypertension nor diabetes, a pulmonary embolus should be suspected. The high incidence of embolic phenomena in the female sex arising from abnormal pelvic conditions is an important factor in this connection. If the history or physical examination brings to light existent or previous evidence of peripheral vascular involvement, *i. e.*, phlebitis, unilateral leg edema, pelvic disease or lower extremity abnormalities, the likelihood of the coronary syndrome being caused by an embolus to the lungs is strengthened.

Occurring postoperatively, the clinical picture of pulmonary embolus readily simulates coronary thrombosis. When it is recalled that pulmonary emboli are very frequent after operation and that coronary artery thrombosis is comparatively rare because patients with coronary artery disease are spared any but emergency surgical procedures, such cases will be correctly analyzed. One should only cautiously advance the diagnosis of coronary thrombosis in a patient presenting the syndrome under consideration who does not give a history suggesting coronary artery disease, *i. e.*, anginal attacks, "gastric" symptoms, etc. Levine<sup>6</sup> was able to obtain such information in the majority of cases he studied and he lays great stress on the value of this data in diagnosis. Pulmonary embolism may explain the syndrome in such an instance.

Finally, in a hyposensitive individual, when the diagnosis of coronary artery thrombosis is made in the absence of pain, and dyspnea is an outstanding sign, the possibility of a pulmonary embolus must be excluded. Here, too, severe dyspnea and marked cyanosis, even in the presence of pain, should direct attention to this diagnosis. For these signs are the most striking and characteristic of pulmonary embolus. The dyspnea is severe, taking the form of rapid stertorous breathing, signifying a genuine air hunger. The cyanosis is usually very marked and usually exceeds that of coronary artery thrombosis. Unfortunately, the location and radiation of the pain in coronary artery thrombosis are so variable that from these features alone in any given case differentiation cannot be made from the intrathoracic pain induced by a pulmonary embolus.

The conditions may coexist, as exemplified in our Cases 1 and 2. Coronary artery occlusion with resulting myomalacia cordis is not infrequently the cause of ventricular mural thrombosis. As the left anterior descending branch of the left coronary artery is the one most commonly involved, and according to Gross<sup>7</sup> supplies

small parts of the right ventricle and the septum, right ventricular mural thrombosis may occur after left coronary artery occlusion. Therefore, pulmonary emboli may readily complicate this condition. When both conditions are present, the association outlined above does not necessarily hold. In both of our cases illustrating this association the origin was not intracardiac, but in the lower extremities. Nevertheless, wherever the emboli arise, the symptoms caused by a pulmonary embolus in a patient who has proved coronary disease may so simulate a coronary occlusion as to be impossible of differentiation. Unless the manifestations of the embolus are typical, with right side chest pain, pleural rubs and hemoptysis, the condition goes unrecognized, to be disclosed only in the pathologic study. Differentiation in this kind of case is perhaps of pure academic interest and it suffices here merely to point out the problem involved.

In addition to the above discussed clinical features, one must consider in the differential diagnosis the help offered by various laboratory investigations. The rise in the leukocyte count which follows coronary thrombosis with infarction of the myocardium also occurs in pulmonary infarction resulting from pulmonary emboli (Libman and Sacks<sup>8</sup>). Thus the blood count cannot be of definite aid in differentiation.

Roentgen ray films of the lungs always serve as an important means of determining the presence of pulmonary lesions. Unfortunately the gravity of the general condition of these patients usually contraindicates this procedure.

To determine differentiating criteria, Anderson<sup>9</sup> recently investigated the electrocardiographic findings in experimentally induced pulmonary embolism in dogs. He found fairly consistent changes such as "tachycardia with disturbance of S-T segments with inverted T waves. Coronary T waves were encountered only once. The work suggests a rather more rigid requirement for the electrocardiographic diagnosis of coronary thrombosis but whether the tracings are sufficiently differentiated to warrant electrocardiographic diagnoses of pulmonary embolism is uncertain." His paper is available only in abstract, but it is safe to say that similar studies should be repeated on man in order to establish the electrocardiographic changes in pulmonary embolism. Pathologic studies must also be undertaken in order to correlate the artery and lung involvement with the electrocardiographic findings.

Aside from the desirability of interpreting the manifestations of disease states as accurately as possible, the differentiation of pulmonary embolization from coronary thrombosis has a practical aspect. Pulmonary emboli have been successfully removed surgically by Kirschner<sup>10</sup> and by Meyer,<sup>11</sup> who used the method first described by Trendelenburg.<sup>12</sup> With improvements in technique and more clearly defined indications, it may be possible in the

future to deal with more of these pulmonary embolic accidents in this radical manner.

**Summary.** Pulmonary embolus may cause a clinical picture indistinguishable from the syndrome of an acute coronary artery thrombosis. The case records and autopsy findings are presented of 6 patients in whom this problem in diagnosis occurred. In 2 the conditions coëxisted. Some points of possible aid in differentiation are discussed. The possibility of successful surgical removal of pulmonary emboli, as well as other differences in treatment, makes this problem more than one of purely academic or diagnostic importance.

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### RENAL AMYLOIDOSIS IN RELATION TO RENAL INSUFFICIENCY.

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MUCH conflicting evidence has been brought forth in the numerous case reports in the literature in which various interpretations have been given to the occasional occurrence of renal insufficiency in renal amyloidosis. Some have regarded the renal insufficiency found at times in amyloidosis of the kidneys as coincidental, and much is said of amyloid admixture with other well recognized forms of renal disease. Others have regarded the occurrence of renal insufficiency as a part of renal amyloid disease itself in its later stages, thus simplifying the pathologic concept in an attempt to explain both physiologic and pathologic changes on the basis of a single disease entity.

In view of the active interest in this subject and the various interpretations given to it in the literature, a study of 100 cases of renal

amyloid disease which came to autopsy in the Philadelphia General and University of Pennsylvania Hospitals during the last 12 years is presented here. Particular emphasis has been placed on the presence or absence of renal insufficiency and the interpretation of its presence in the light of the gross and microscopic appearance of the kidneys.

**Method of Study.** One hundred unselected cases of renal amyloidosis were studied and correlated with the clinical records, including a survey of the various underlying etiologic diseases, age incidence, blood pressure readings, weight of heart, presence or absence of edema, urinalyses, blood chemical studies and other clinical evidences of renal insufficiency.

In the 9613 autopsies performed between the years 1920 and 1932, amyloid was found in the kidneys in exactly 100 cases. In this series renal amyloidosis was found to occur between the ages of 11 and 82, with the highest incidence in the 3d decade (Table 1). In 2 instances, amyloid was found in the kidneys and not in the liver or spleen, contrary to the more common finding of extensive deposits of amyloid in the latter organs with little or none in the kidneys.

Chronic ulcerative pulmonary tuberculosis was found in 70 per cent of the cases, which is in keeping with the well known fact that the most common cause of amyloidosis is chronic suppuration, particularly that secondary to and implanted upon tuberculosis. The incidence of the probable etiologic diseases in the remainder of the cases is shown in Table 2. The clinical duration of the etiologic disease was 1 year or more in 64 cases, while in 8 cases the duration was 6 months to 1 year. Eight patients gave a history of having had the etiologic disease for a period of only 3 to 6 months. In the remainder of the cases no definite history was obtained as to the duration of the disease which was considered to be the cause of the amyloidosis.

TABLE 1.—AGE INCIDENCE  
(Number and Per Cent).

11 to 20 years . . . . .	9
21 to 30 years . . . . .	27
31 to 40 years . . . . .	18
41 to 50 years . . . . .	19
51 to 60 years . . . . .	13
61 to 70 years . . . . .	9
71 to 82 years . . . . .	5

TABLE 2.—ETIOLOGIC DISEASE  
(Number and Per Cent).

Pulmonary tuberculosis . . . . .	70
Tuberculosis of bone . . . . .	8
Malignant tumors . . . . .	9
Empyema . . . . .	5
Chronic arthritis . . . . .	2
Chronic osteomyelitis . . . . .	1
Bronchiectasis . . . . .	1
Lung abscess . . . . .	1
Cause unknown . . . . .	3

Blood urea nitrogen determinations were made in 46 of the 100 cases. As is shown in Table 3, 34 cases had readings below 35 mg. per 100 cc. In 5 the blood urea nitrogen ranged from 40 to 60 mg., and in 3 from 61 to 100 mg. In only 4 cases was the blood urea nitrogen over 100. Those which showed a blood urea nitrogen of over 35 mg. per 100 cc. were arbitrarily considered as cases associated

with renal insufficiency. Of the 46 cases 12 had this evidence of impaired renal function. How many of the remaining 54 would have shown an elevation in the blood urea nitrogen, had blood studies been carried out, it is of course impossible to say. However, no evidence is given in the clinical record or clinical diagnosis of these 54 cases to suggest that renal insufficiency existed, and it is perhaps for this reason that blood studies were not made. This omission, as well as omissions of adequate blood pressure readings, other renal function tests and complete urinalyses are indeed unfortunate, yet they must be expected in making a retrograde study of such a series of cases.

TABLE 3.—BLOOD UREA NITROGEN DETERMINATIONS (46 CASES).

	Cases.	Per cent.
Below 20 mg. per 100 cc. . . . .	26	56
Between 20 and 30 . . . . .	7	15
31 and 35 . . . . .	1	2
36 and 40 . . . . .	1	2
41 and 60 . . . . .	4	9
61 and 100 . . . . .	3	6
Over 100 . . . . .	4	9

Blood pressure readings were recorded in 35 cases (Table 4). Of these, 20 had a systolic pressure below 120, 11 had a systolic pressure between 120 and 150 and in 4 the systolic pressure ranged from 150 to 180. If a systolic pressure above 150 is taken as evidence of arterial hypertension, this condition may be said to have existed in 12 per cent of the 34 cases. In the 4 cases in which hypertension occurred, the kidneys showed arteriolar nephrosclerosis of moderate degree. In 1 case a large amount of amyloid was present in the kidneys and there was evidence of impairment of renal function as shown by a blood urea-nitrogen reading of 162 mg. per 100 cc. In the other 3 cases amyloid was present in relatively small amounts and there was no evidence to show that renal insufficiency existed.

TABLE 4.—BLOOD PRESSURE READINGS.

	Cases.	Per cent.
Below 120 (systolic) . . . . .	20	57
Between 120 and 150 . . . . .	11	31
Between 150 and 180 . . . . .	4	12
Total cases. . . . .	35	

The phenolsulphonaphthalein excretion was definitely impaired in only 2 of the 5 cases in which this test was performed. Three showed an excretion of over 50 per cent of the dye in 2 hours, while in the other 2 cases the percentage of the excretion was 33 and 15 respectively.

Blood creatinin determinations were made in 7 cases (Table 5) and of these 5 showed 3 mg. or less per 100 cc. In 2 cases the readings were 5.3 and 10 mg. An analysis of the table shows that in only 2 instances was there a definite elevation of both the blood creatinin

and the blood urea nitrogen. As was to be expected, in the 3 cases in which the blood urea nitrogen was only moderately elevated, the creatinin readings were within normal limits.

TABLE 5.—COMPARISON OF B. U. N. AND CREATININ READINGS (7 CASES).

B. U. N., mg. per 100 cc..	Creatinin, mg. per 100 cc..
12	1.3
20	1.2
40	1.6
60	2.3
70	3.0
102	5.3
150	10.0

Qualitative tests for albumin in the urine were recorded in 84 cases. No albumin was found in 7; the remainder (92 per cent) showed albumin varying in quantity from a trace to large amounts.

The specific gravity of the urine was recorded in 72 cases. Twenty-three (32 per cent) showed readings all below 1.020. A specific gravity of 1.020 or greater was observed in the remainder of the cases.

The urine had been examined for casts in 63 cases. These were found to be present in 50 cases (79 per cent), while in 13 (21 per cent) they were absent. In most instances, no mention was made in the records as to the number or kinds of casts seen and no attempt has been made therefore to correlate these in the present survey.

Edema was mentioned as present in 24 of the 100 cases. In most instances, it was slight and confined principally to the lower extremities.

Table 6 gives an analysis of 91 cases in which the combined kidney weight was recorded. These weights, averaging 391 gm., are in keeping with the usual finding that in amyloid disease the kidneys are larger than normal.

TABLE 6.—COMBINED KIDNEY WEIGHTS.

	Grams.	Cases.	Approximate per cent.
Below 200		2	2
Between 200 and 300		20	22
301 and 400		33	36
401 and 500		23	25
501 and 600		6	6
601 and 700		3	3
701 and 800		4	4

The size of the heart was usually small or within normal limits (Table 7). If 350 gm. is taken as the upper limit of normal, then 16 cases showed cardiac hypertrophy. In 5 of these, cardiac lesions were found which could well account for this hypertrophy without invoking renal amyloidosis as a cause: 2 had pericardial adhesions, 2 mitral stenosis and 1 had aortic insufficiency.

Since this study is primarily concerned with the occurrence of renal insufficiency in amyloidosis of the kidneys, especial attention

was paid to cases which gave evidence of impairment of renal function. The basis for considering that renal insufficiency existed was an elevation of the blood urea nitrogen above 35 mg. per 100 cc. Data on blood creatinin, phenolsulphonephthalein excretion and the concentrating power of the kidneys were not complete enough to be cited as evidences of renal insufficiency. On the basis of the

TABLE 7.—HEART WEIGHTS IN 100 CASES.

Grams.	Cases.
150 to 250 . . . . .	51
251 to 350 . . . . .	33
351 to 400 . . . . .	4
401 to 500 . . . . .	8
501 to 600 . . . . .	2
Over 600 . . . . .	2

standard above noted, 12 cases of renal amyloidosis were found to be associated with renal insufficiency (Table 8).

The 12 cases associated with renal insufficiency were studied in detail both grossly and histologically in an attempt to learn if amyloid disease itself, in its later stages, can account for renal insufficiency without admixture of other bilateral inflammatory or degenerative disease of the kidney. Several stains were employed: hematoxylin and eosin, methyl violet and Congo red; the latter two being specific stains for amyloid.

With experience, it is usually not difficult to separate the characteristic microscopic picture of renal amyloidosis causing impairment of kidney function from that of other kidney disease usually associated with renal insufficiency. Seven (Nos. 1, 5, 7, 8, 9, 10, 12) (Table 8) of the former type were found after a thorough review of the sections from the kidneys of the above 12 cases. The histologic picture was correlated with the gross description of the kidneys. The kidneys were of average size or moderately enlarged, firmer in consistency than normal and the cortical surface was uniformly coarsely granular and pale gray in color. The resistance to cutting was definitely increased and the cut surface was pale gray and fibrous in appearance. In some instances the cortex was not distinguishable from the medulla, while in others the cortex was moderately narrowed and fairly well demarcated from the medulla.

Microscopically, the architecture was greatly altered by an irregular overgrowth of dense fibrous tissue which was infiltrated with a few lymphocytes, and occasionally contained homogeneous material which gave the amyloid staining reaction. Most of the glomeruli were filled with amyloid which completely obliterated the capillary bed. These glomeruli were considerably increased in size, some up to twice normal. A few were of average size and contained relatively small amounts of amyloid, which appeared to obstruct only a few of the capillaries of the tuft. In a few sections the glomeruli containing amyloid showed moderate thickening of



TABLE 3.—SUMMARY OF 12 CASES SHOWING RENAL INSUFFICIENCY.

Series No.	Autopsy No.	Etiologic disease.	Duration (yrs.)	Age.	Sex.	Col.	Blood urea N (mg.).	Creati- tinin (mg.).	P.S.P.	B. P.	Urine.			Weight heart (gm.).	Comb. weight kidneys (gm.).	Edema.
											Sp. gr.	Alb.	Costs.			
1	31-662	Tbc. of hip	8	40	M.	W.	180	...	...	104/60	....	...	....	290	290	0
2	30-213	Arthritis deformans	12	43	M.	W.	70	...	...	....	....	+	....	500	715	0
3	30-31	Chr. osteomyelitis	7	27	M.	W.	102	5.3	...	....	1010	Trace	+	210	525	0
4	29-121	Chronic arthritis	11	41	M.	W.	150	10	...	106/58	1015	++	....	350	360	0
5	27-195	Pulmonary Tbc.	4	19	F.	W.	50	...	...	130/90	1019	0	+	190	520	+
6	24-123	Hypernephroma	2	56	M.	W.	162	...	...	175/95	1022	+	+	450	550	0
7	24-19	Pulmonary Tbc.	1	61	M.	W.	60	2.3	...	95/45	....	..	....	350	320	0
8	23-567	Pulmonary Tbc.	1½	21	M.	B.	40	1.6	13%	....	1020	++	++	240	430	0
9	31-125	Lung abscess	?	33	M.	B.	65	...	...	100/80	....	++	++	390	490	0
10	20-392	?	?	19	M.	W.	72	...	...	118/90	1010	++	....	320	650	Slight.
11	32-34	Pulmonary Tbc.	2	34	M.	W.	45	...	...	80/40	....	++	....	150	300	0
12	31-827	Pulmonary Tbc.	?	65	M.	W.	.70	3	...	110/70	1009	+++	....	300	340	0

the capsule of Bowman, but "crescent formation" was not noted, although there were adhesions between the tuft and the capsule. In the areas of dense fibrosis there was marked atrophy or complete disappearance of the tubules. These were thought to represent in large part the tubules leading from the glomeruli which were damaged or destroyed. In the areas where the fibrosis was not so marked, the tubules were greatly dilated and the lining epithelium was flattened. Casts were seen in many of the tubules. A few sections showed the medulla to contain deposits of amyloid around the tubules and in the walls of the small arteries. Some of the sections showed the walls of the larger arteries to be moderately thickened, but this change was most marked in the arterioles. Material which stained for amyloid was seen in the walls, causing the lumina to be narrowed.

This histologic picture of renal amyloidosis in its late stages is similar in some respects to that of the small granular kidney of chronic glomerulonephritis and in the later stages of arteriolar nephrosclerosis, mainly in the alteration of the architecture by the irregular overgrowth of fibrous tissue in the stroma, lymphocytic infiltration in the patches of fibrosis, and dilatation or atrophy of tubules.

In late amyloid disease resulting in renal insufficiency, amyloid is present in such massive amounts that the capillary bed of many glomeruli is occluded. The glomeruli containing amyloid are somewhat larger than normal and as a rule there is slight thickening of the capsule of Bowman and no proliferation of the cells of the glomerular tuft. The walls of the arterioles are definitely thickened and their lumina are narrowed; but in no case is complete obliteration of the lumen observed. The amyloid deposits are characteristically found in the media of the arterioles and the thickening of the wall of the vessel as a result of amyloid deposits in this coat results in narrowing of the lumen. In chronic glomerulonephritis the characteristic picture is the change in the glomeruli which are shrunken and often appear as balls of fibrous tissue showing complete or partial hyalinization and marked thickening of the capsule of Bowman. In advanced arteriolar nephrosclerosis, the arteriolar changes are conspicuous. The walls of the afferent arterioles are thickened and the lumina greatly narrowed and often completely obliterated. Here the thickening is the result of intimal sclerosis, while in the advanced stage of renal amyloidosis the thickening is principally the result of deposition of amyloid in the media of the vessels. In addition, the glomeruli show lobulation of the tufts, with slight thickening of the walls of the individual capillaries, and often present changes similar to those already described for chronic glomerulonephritis which result secondarily from loss of blood supply to them, due to occlusion of the afferent arterioles.

If all these facts are borne in mind, one can almost follow the pathogenesis of changes in the kidney, which finally result in insufficiency. It will also be seen that as each of the three conditions (amyloidosis, glomerulonephritis, arteriolar nephrosclerosis) increases in severity, the histologic pictures become more and more alike and difficult of separation, because the change which is common to them all, namely, the replacement fibrosis, becomes even more marked.

The remaining 5 of the 12 cases showing renal insufficiency could not with justification be classified in the group in which the renal insufficiency was attributed to the amyloid itself. Two of these (Cases 2 and 6) presented a picture so much like that of arteriolar nephrosclerosis, with a history and clinical findings that suggested antecedent nephrosclerosis, that the latter was regarded as the essential factor in the production of the renal insufficiency. The other 3 cases (Nos. 3, 4, 11) could not be classified from the standpoint of the histologic picture, not having either sufficient amyloid or the picture of non-amyloid renal disease to be placed in either of the above categories.

**Discussion.** It is generally believed that the occurrence of azotemia is relatively infrequent in amyloid disease of the kidneys. However, in this series of cases the condition occurred in 26 per cent of the 46 cases in which blood chemistry studies were made. Studies of the material from these cases corroborate the view of 'Troisier and his coworkers' that renal amyloidosis may manifest itself in several ways and that other degenerative and inflammatory diseases of the kidney may be simulated by amyloidosis in one or more of its stages. The main factor in the development of renal symptoms would appear to be the amount and extent of amyloid deposit in the kidneys. With little amyloid in the glomerulus there may or may not be enough injury to the glomerular capillaries to allow albumin to escape into the urine. With larger deposits of amyloid, there is more extensive injury to the glomerular capillaries and a larger amount of albumin escapes. In some instances the loss of this protein is great enough to result in a lowering of the osmotic pressure of the plasma, so that edema occurs. When the amyloid deposits are extensive, destruction of varying amounts of the renal parenchyma follows and renal insufficiency may ensue.

The destruction of the renal tissue and its replacement by fibrous tissue is apparently the result of obstruction of the afferent arteriole or occlusion of the capillaries of the glomerular tuft by deposits of amyloid. The tubules leading from destroyed glomeruli undergo atrophy and are replaced by fibrous tissue which results in a scarred and more or less contracted kidney similar in many respects to an advanced arteriolar nephrosclerosis or the late stage of chronic glomerulonephritis. Noble and Major<sup>2</sup> state that the pathologic process by which the kidneys in amyloid disease reach the state of

renal insufficiency shown in their cases is primarily one of vascular damage affecting the glomeruli most severely, but also involving the arteries of small caliber. They found the lumina of the afferent arterioles narrowed and the walls thickened by amyloid deposits, but in no case did they observe complete occlusion of the arterioles. In the present series, several cases were found which showed no significant changes in the afferent arterioles, while there were large deposits of amyloid in the glomeruli; which corroborates the view of these workers that the presence of amyloid in the glomerulus is the primary factor in the obstruction of the glomerular circulation, and in the resulting damage to the kidney and renal insufficiency.

In cases of renal insufficiency occurring with renal amyloidosis, the kidneys are usually described as being shrunken and scarred as a result of the extensive deposits of amyloid. None of the 12 cases of renal insufficiency in this series showed a reduction in the size of the kidneys. In 2 reported by Noble and Major, the kidneys showed no evidence of contraction and were unusually large. They considered the deposition of amyloid to have been so rapid that closure of capillaries and resulting azotemia occurred before contraction could take place.

The factors which enter into the clinical diagnosis of renal amyloidosis seem to be very variable, and it is not surprising that often the condition is not recognized until the patient comes to autopsy. Chronic glomerulonephritis is perhaps the most common diagnosis made in cases of unrecognized renal amyloidosis, especially when there is no apparent underlying disease to make one suspect the existence of amyloidosis. This was found to be true both in studies in the literature and in the cases studied in this survey. The material from these cases also supports Rosenberg's<sup>3</sup> statement that in the late stage of amyloid disease of the kidney the patient may run a course similar to that of the end stage of chronic glomerulonephritis with edema, slowly progressing renal insufficiency and an increasing azotemia. In amyloid disease, however, there is no hypertension or hypertrophy of the heart and nitrogen retention is not so marked as in chronic glomerulonephritis.

Bannick and Barker<sup>4</sup> state that renal amyloidosis has a clinical picture similar to that of chronic nephrosis but usually differs somewhat by the greater reduction in the excretion of phenolsulphoncphthalein and in that there is likely to be some hematuria. They regard edema, hypercholesterolemia and hypoproteinemia as variable factors. The presence of hematuria, extrarenal sources of the blood being ruled out, eliminates the diagnosis of nephrosis. Christian<sup>5</sup> states that definite hematuria occurring in a patient showing the clinical picture of chronic nephrosis strongly indicates a definite form of glomerulonephritis. Abrami, *et al.*<sup>6</sup> found progressive azotemia possible, although exceptional, as the only manifestation of renal amyloidosis.

This study also supports Brulé's<sup>7</sup> contention that there is no special symptomatology of renal amyloidosis, as it is frequently associated with lipid nephrosis and is often found in kidneys which show the lesions of glomerulonephritis. Sliapiro<sup>8</sup> considers lipid nephrosis and amyloidosis to be independent conditions and that either may be far advanced without the other existing. He states that amyloidosis when superimposed on lipid nephrosis contributes to the renal damage and renders the prognosis grave. Abramí and his coworkers<sup>9</sup> feel that changes in the blood proteins and lipins are independent of the development of the amyloid process, since these changes are found with equal frequency in patients who do not have amyloid disease.

Polyuria is given as one of the early symptoms of renal amyloidosis by Labbé, *et al.*,<sup>10</sup> but this symptom may also be a prominent feature of arteriolar nephrosclerosis and chronic glomerulonephritis. According to Ellis and Weiss<sup>11</sup> the reabsorbing ability of the tubules may be impaired as a result of direct structural damage to the tubular cells themselves, and also as the result of conditions whereby excessively large amounts of glomerular filtrate pass rapidly down the tubules. They used as an example of the latter situation the kidneys in nephrosclerosis in which one-half of the glomeruli might be obliterated while the remainder would be comparatively unaffected. The normal glomeruli would greatly increase their individual filtration but this filtrate would be passing down one-half the usual number of tubules and the reabsorption of water would be decreased. The polyuria of renal amyloidosis can be similarly explained. In the present series there was not sufficient evidence on this point to warrant discussion.

The presence of albumin in the urine is a very common occurrence in renal amyloidosis (92 per cent in this series), and in a case with a suggestive disease background such as chronic tuberculosis, it may suggest amyloidosis, but of course is not sufficient in itself for a positive diagnosis. The common occurrence of albuminuria in all types of kidney disease makes it one of the least significant signs in the differential diagnosis of renal amyloid disease. Borrromeo<sup>12</sup> considers variations in the amount of albumin in the urine to be important evidence of the presence of amyloid in the kidney. He reports a case in point which also had definite signs of cardiac decompensation with chronic passive congestion of the kidneys. The latter could easily have accounted for fluctuations in the amount of albumin in the urine.

**Summary.** 1. In 9613 consecutive autopsies, 100 cases of renal amyloidosis were found.

2. Tuberculosis of the lungs (70 per cent) and bones (8 per cent) was the etiologic disease in 78 per cent of the cases.

3. The highest incidence of renal amyloidosis occurred in the third decade of life.

4. Twelve of the 46 cases in which sufficient evidence was available were associated with renal insufficiency.

5. Obstruction of the glomerular capillaries by amyloid deposits is a factor in the causation of renal insufficiency.

6. Hypertension is relatively infrequent in amyloid disease of the kidney. Of 35 cases with blood-pressure readings, the systolic pressure was above 150 mm. in only 4 (12 per cent).

7. In the cases of renal amyloidosis with renal insufficiency, the kidneys were either normal in size or somewhat enlarged.

8. Renal amyloidosis may occasionally be associated with independent arteriolar nephrosclerosis.

9. Albuminuria is a fairly constant finding in renal amyloidosis.

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## REVIEWS.

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**INDUSTRIAL HEALTH SERVICE.** By LEVERETT DALE BRISTOL, M.D., Dr.P.H., Health Director, American Telephone & Telegraph Co., New York City; formerly Commissioner of Health of the State of Maine, and Professor of Preventive Medicine and Public Health, University of Minnesota. Pp. 170. Philadelphia: Lea & Febiger, 1933. Price, \$2.00.

THIS little book, which treats of the establishment and the management of an industrial health service, is written for the factory superintendent rather than the physician, but contains much which the physician starting in industrial work will find of value. The first part develops a well-balanced industrial health program. Parts II and III are suggestions as to management in the health instruction and problems of workers. Written in terse, simple style, the points are clearly presented. The author emphasizes particularly the importance of the public health aspect of medical supervision in industrial work and outlines the steps which will make this most effective.

The author believes that the management group in industry may participate actively in the health program and devotes considerable space in pointing out how this may be done. The short chapters which deal with common diseases and conditions common among workers might readily be used in health bulletins for general distribution in the factory.

W. C.

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**SURGICAL ANATOMY.** By GRANT MASSIE, M.B., M.S. (LOND.), F.R.C.S. (ENG.), Assistant Surgeon, Guy's Hospital, etc. Pp. 458; 147 illustrations, many in color. Second edition. Philadelphia: Lea & Febiger, 1933. Price, \$6.00.

A CONCISE and useful treatise on practical anatomy brought up to date. It should prove to be of interest to the student and general surgeon. The many illustrations are, for the most part, diagrammatic but none the less clear and informative. Confusion of nomenclature has been avoided by employment of both the old and the B. N. A. terminology.

G. W.

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**DIETETICS FOR THE CLINICIAN.** By MILTON ARLANDEN BRIDGES, B.S., M.D., F.A.C.P., Associate in Medicine at the New York Post-Graduate Medical School, Columbia University, in collaboration with RUTH LOTHROP GALLUP, Dietitian. Foreword by HERMAN O. MOSENTHAL, A.B., M.D., Director of Medicine at the New York Post-Graduate Medical School, Columbia University. Pp. 666; 31 tables. Philadelphia: Lea & Febiger, 1933. Price, \$6.50.

THE first 70 pages are devoted to the mechanics and physiology of digestion; the vitamin factors in diet; the classification, distribution and composition of foods; foods from the culinary standpoint. Then follow 465 pages on diet in specific diseases and conditions (alphabetically arranged) and on dietetics in pediatrics. (Some 18 physicians working in

various fields of clinical medicine have aided in preparing this part of the book.) The appendix (65 pages) contains recipes, information on supplementary methods of food and fluid administration; numerous tables (food composition, height and weight data, etc.).

Written for the general practitioner and the hospital intern, the subject matter is accurate, adequate, eminently practical and well presented. The book deserves emphatic recommendation.

R. K.

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THE GREAT DOCTORS. A Biographical History of Medicine. By HENRY E. SIGERIST, Professor of the History of Medicine, The Johns Hopkins University. Translated by EDEN and CEDAR PAUL. Pp. 436; illustrated. New York: W. W. Norton & Co., Inc., 1933. Price, \$4.00.

IN 1931, the author published from Lehmann's house in Munich his "Grosse Aertze," a successful attempt to sketch the history of medicine through the portrayal of the lives of 55 leaders—from Imhotep to Ehrlich. To this translation, which has already had 3 printings in 1 year, another figure has been added—William Osler. Illustrative of the method is the division of the Osler section into 3 pages of development of the theme, "America entered the medical stage," and 3 more of a few salient details of Osler's life with a warm but correct appreciation of his influence. Like Lenard's "Grosse Naturforscher" and Almquist's "Grosse Biologen" in the same series, this work makes full use of the interest that all men have in personalities. While the author's method and charming style combine to make it interesting to lay and professional readers alike, his scholarship and scientific conscience keep the story from falling into the inaccuracies that mar so many recent popularized biographies.

E. K.

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SPEECH DISORDERS. A Physiological Study of the Various Defects of Speech. By SARA M. STINCHFIELD, PH.D., Lecturer in Psychology, University of Southern California, Speech Clinic, Orthopaedic Hospital School, Los Angeles. Pp. 341, 8 plates of illustrations. New York: Harcourt, Brace & Co., 1933. Price, \$4.00.

IN the opinion of this author, surveys indicate an increase of speech disorders. The text is divided into two parts. Part I includes a classification covering more than four pages (two disorders taken at random are rhinolalia uranosehismatica and paraphonia eunuehoidia). A chapter on Dysarthria Cerebropathica contains a large group of neuropsychiatric diseases. Part II gives statistical studies of the speech of 3000 college women and of public school groups. An interesting chapter is Personality, considered as Thurstone Personality Schedule and Trait Inventory. By reason of their fewer social distractions, Thurstone finds that neurotic students outstrip their well-adjusted classmates. The book is a useful contribution to speech literature.

N. Y.

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NEW INTRODUCTORY LECTURES ON PSYCHOANALYSIS. By SIGMUND FREUD, M.D., LL.D. Pp. 257; 1 illustration. New York: W. W. Norton & Co., Inc., 1933. Price, \$3.00.

CONTINUING and supplementing earlier lectures, this volume considers dreams, the occult, anatomy of the mental personality, anxiety and instinctual life, psychology of women and a philosophy of life. Telepathy and thought transference, while not definitely endorsed, thread their way



through 27 pages of the text. The author complains that he is charged with things never said, such as, "the statement that all dreams are sexual." This seems to have been almost universally misunderstood.

The association tests of Jung are not mentioned and he cannot accept in its entirety the inferiority complex of that constructive analyst, Adler. Though names are prudently withheld, the following identities are unmistakable. Biographer Ludwig holds the withered arm of the ex-Kaiser responsible for an inferiority complex, said to figure so largely in the latter's psychologic life. The author differs, saying, instead of an excess of love that would naturally be accorded a disabled child, the proud mother withheld this love, which, in turn, caused the development of a relentless aversion toward the mother.

The charge that the author borrowed from Buddha on libido, from Plato on dreams and from others may show his good judgment. His presentations have taken hold on modern thought, and candor compels one to admit the desirability of psychoanalysis with modifications, in selected subjects, for a better understanding of certain cryptic thoughts, utterances and actions.

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THE DIAGNOSIS AND TREATMENT OF DIABETES. By W. WILSON INGRAM, M.C., M.D. (ABER.), Honorary Physician and Physician in Charge of the Clinic for Diabetes Mellitus, Royal North Shore Hospital, Sydney, etc.; and G. V. RUDD, M.Sc. (MELB.), Research Biochemist, Institute of Medical Research, Royal North Shore Hospital, Sydney. With a Preface by C. G. LAMBIE, M.C., M.D., F.R.C.P., F.R.S.E., Bosch Professor of Medicine, University of Sydney. Pp. 88; illustrated. Australia: Angus & Robertson, Ltd., 1933. N. Y.

This small manual on diabetes and its treatment is unusual in that it is written for the physician and not the patient, with consequent omission of much elementary explanation. The chapters are devoted to definition, clinical considerations, laboratory diagnosis, diets, insulin and complications. While the subject matter is well and clearly presented, the small size of the book has resulted in some subjects being inadequately treated: 3 pages seem hardly enough for so important a part of diabetes as acidosis and coma. Seven set diets are given, ranging from 1100 to 2600 calories, with a list of foods, equal in value to a slice of bread, to be used for varying these diets.

The book is well worth reading even though it is written for use in Australia and the diets are arranged to suit the needs of people living in that climate. R. R.

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DE VENARUM OSTIOLIS 1603 OF HIERONYMUS FABRICIUS OF AQUAPEN-  
DENTE (1533?-1619). Facsimile edition with Introduction, translation  
and Notes by K. J. FRANKLIN, D.M., Tutor and Lecturer in Physi-  
ology of Oriel College and University Demonstrator of Pharmacology,  
Oxford. Pp. 98; illustrated. Springfield, Ill.: Charles C Thomas,  
1933. Price, \$3.00.

Those who are fortunate enough to own an annotated translation and facsimile edition of Harvey's *De Motu Cordis*, such as Leake's edition put out by Thomas in 1928, should require no further stimulus toward the purchase of this work by Harvey's teacher. His detailed description and public demonstration at Padua of the valves in the veins (discovered a half century earlier) was undoubtedly one of the most important links in the chain of Harvey's argument. The present book, published by the History of Science Society, with the aid of a grant from the Carnegie

Corporation, includes an interesting biographic notice of Fabricius, accounts of early studies of the venous valves, and of the Anatomical Theatre at Padua, as well as a Bibliographic Note on the difficulties met in establishing the first edition of Fabricius' work.

E. K.

NEUROLOGY. By ROY R. GRINKER, M.D., Associate Professor of Neurology, The University of Chicago. Pp. 979; 401 illustrations. Springfield, Ill.: Charles C Thomas, 1934. Price, \$8.50.

THIS is the best recent book on neurology in English that we have seen. Logically conceived and structurally sound, it presents the subject as one phase of biology, rather than a dry detailing of the cause, pathology, symptoms, diagnosis and treatment of each nervous disease. Pains are taken to correlate structure and function as much as possible. It contains up-to-date information on such subjects as the histopathology of tumors, spinal fluid function and analysis, intracranial pressure, epilepsy, encephalitis, etc. The significance of the work of Sherrington and Magnus on reflexes is ably presented. The tables and diagrams are excellent and the illustrations well selected and well reproduced. The bibliography at the end of each section refers accurately to not only treatises but also specific monographs and journal articles. The index is accurate, as far as can be determined.

E. T.

GREAT MEN OF SCIENCE. A History of Scientific Progress. By PHILIPP LENARD, formerly Professor of Physics and Director of the Radiological Institute in the University of Heidelberg; Nobel Laureate; Rumford Medallist of the Royal Society of London; Franklin Medallist of the Franklin Institute of Philadelphia. Translated from the second German edition by DR. H. STAFFORD HATFIELD. With a Preface by E. N. DAC. ANDRADE, Quain Professor of Physics in the University of London. Pp. 389; illustrated. New York: The Macmillan Company, 1933. Price, \$3.00.

To those who accept that the history of medicine is inextricably interwoven with the history of science no excuse need be given for reviewing this book, even though Leonardo da Vinci is the only one of the 65 scientists whose work bears directly on medicine. Linnæus, J. R. Mayer, and Helmholtz, the only ones who appear to have completed medical studies, are all of the elect for their contributions to related subjects only. While it is perhaps chastening to physicians to realize how few of their own profession are included in such a list, and perhaps surprising to be reminded that other sciences have more claim than we to such familiar names as Boyle, Descartes, Newton, Black, Priestley, Darwin and others, still one might well ask why Hippocrates, Galen, Vesalius, Harvey, Morgagni, Bichat, Virchow and others did not have a right to be included. In a goodly company of chemists, Lavoisier is notable for his absence, though his name perforce appears often in the index.

The author, a distinguished pupil of Bunsen's and a Nobel Prize winner in physics, has succeeded in combining in a short space clear accounts of the contributions of these great men with personal pictures that present to us living personalities, sometimes human beings in error, but always struggling with more or less equanimity at their appointed problems toward the truth. To physicians the book may well be more stimulating than if more directly linked with their own field.

E. K.

VERHANDLUNGEN DER DEUTSCHEN GESELLSCHAFT FÜR KREISLAUFFORSCHUNG. VI. Tagung. Gehalten zu Würzburg am 6. und 7. März, 1933. By PROFESSOR DR. BRUNO KISCH, Köln. Pp. 276; 97 illustrations and 35 tables. Leipzig: Theodor Steinkopff, 1933. Price, Rm. 15.—

IN this sixth volume, according to the plan followed in this series (see Review, AM. J. MED. SCI., 1933, 185, 427) whereby emphasis is laid on a certain phase of the problem, the relation of the nervous system is stressed. The chief addresses were by H. E. Hering, representing the laboratory side and F. Kauffmann for the clinical side. Studies in the most varied channels of this field are represented in 26 other articles. E. K.

HISTOLOGY. By S. RAMÓN-CAJAL, M.D. (MADRID), F.R.S. (LONDON), LL.D. (CLARKE), Director, Royal Cajal Institute for Medical Research; Emeritus Professor of Pathology, University of Madrid Faculty of Medicine; Nobel Premiate in Medicine; Life Senator of Spain. Revised by J. F. TELLO-MÚÑOZ, M.D. (MADRID), Professor of Pathology, University of Madrid Faculty of Medicine. Authorized translation from the tenth Spanish edition by M. FERNÁN-NÚÑEZ, M.D. (MADRID), Professor of Pathology, Marquette University Medical School. Pp. 738; 535 illustrations. Baltimore: William Wood & Co., 1933. Price, \$8.00.

THIS translation is a welcome addition to current texts on the subject, both because of the novelty of many of the illustrations and of its fuller treatment of cytologic and neurohistologic topics. It offers the student of medicine his first opportunity of becoming acquainted, in English, with at least one aspect of the many-sided activities of the great Spanish histologist. Although the author has always been interested primarily in the nervous system, there is no part of the body which he and his students have not investigated by original methods. These results are reflected here, especially in the description of the tissues, which compose the major part of the book. The methods of general histology as well as those applicable to the nervous system are given ample . . . . . pages. These include the reduced silver methods for neurofibrils, in which the tissues are first immersed in silver nitrate, and then in a photographic developer, such as pyrogallol acid, when silver salts are formed within the nerve tissues. Nine methods for demonstrating neuroglia are given, among them those of Cajal, Río-Hortega and Schüecarro. In all the descriptions, one sees the careful attention to detail, characteristic of the Madrid school.

W. A.

CLINICAL SCIENCE INCORPORATING HEART. VOL. I, No. 1. Edited by THOMAS LEWIS, M.D., F.R.S., aided in the selection of papers by T. R. ELLIOTT, M.D., F.R.S., R. T. GRANT, M.D., P. P. LAIDLAW, F.R.S., EDWARD MELLANBY, M.D., F.R.S., WILFRED TROTTER, M.S., F.R.S., and E. B. VERNEY, F.R.C.P. Pp. 158; illustrated. London: Shaw & Sons, Ltd., 1933. Price, 37/6.

*Tempora mutantur* and, of course, the publishers are wise in changing the name of this well-known journal to conform with the wider scope of its articles, even though for some time "related topics" have appeared happily under the old title. One always parts regretfully from an old friend, and it is perhaps with this as well as more practical considerations in mind that the publishers have maintained "Heart" in the largest letters on the cover. Of the 6 articles in this initial number—all from the University College Hospital—only 2 deal directly with cardiac problems.

E. K.

**LIFE IN THE MAKING.** By DR. ALAN FRANK GUTTMACHER, Associate in Obstetrics, Johns Hopkins University. With the assistance of ELLERY RAND. Pp. 297; 8 illustrations. New York: The Viking Press, 1933. Price, \$2.75.

WITH the gradual lifting of the sex tabu that this century is witnessing, the natural human interest in the generative process will, of course, evoke books of all grades. Unless we are willing to let the latrine method of diffusing information be replaced by equally reprehensible pornographic printed material, it behooves us to support such books as this, written in a dignified, accurate, instructive yet interesting style, by one whose professional position is in itself a guarantee. A judicious mixture of the historical approach (chiefly incorrect superstition) and modern science, with frequent reference to lower animals, has allowed the author to achieve his aim of offering in a readable way knowledge of a vital process which human beings should understand. The subject matter is divided into six parts: How Life Begins; Sexual Rhythms; Male and Female Sex Determination; Sterility and Fertility; Twins. In the interesting account of conjoined twins, it should be stated that examination of the original Siamese twins was concluded at the Mütter Museum of the College of Physicians (not of the University of Pennsylvania, as stated).

E. K.

**A THEORY OF THE FORMATION OF ANIMALS.** By W. T. HILLIER, M.R.C.S., L.R.C.P. Pp. 166; 98 text illustrations and 7 full-page plates. Baltimore: William Wood & Co., 1933. Price, \$3.00.

THIS develops Laurence Oken's theme that every animal really consists of two animals, a "capital" and a "genital," using, of course, better evidence and arguments than were available in the early 19th century. The fore limbs belong to the head animal, the hind limbs to the other; the salivary gland to the former, the pancreas to the latter and so on. The dual constitution of the fertilized ovum and the two layers of the gastrula are invoked and examples taken from the annelid *Polygordius* and the common herring. The book attempts thus to explain the formation especially of genera but is not convincing.

E. K.

**MATERNAL MORTALITY IN NEW YORK CITY.** A Study of All Puerperal Deaths, 1930-1932. By the New York Academy of Medicine Committee on Public Health Relations. By RANSON S. HOOKER, M.D., F.A.C.S. Director of the Study. Pp. 290; 89 tables. New York: The Commonwealth Fund, 1933. Price, \$2.00.

IN this study, 2041 deaths were reviewed, of which 1343 (65.8%) were held to have been preventable. In the latter group, the physicians were adjudged responsible in 61.1%, patients in 36.7 and midwives in 2.2; indeed, an indictment of and a challenge to the medical profession of New York. Among the factors relating to the physician's responsibility may be mentioned incompetency, lack of judgment and skill, and carelessness. Unsupervised activity of interns is regarded as an appreciable factor. Failure on the part of patients to avail themselves of facilities freely offered, and their lack of cooperation, contributed more than one-third of the deaths.

The subject of preventability is thoroughly discussed, with illustrative case histories under various headings. In a review of the principal causes of death are included the influence of anesthesia, operative delivery, Cæsarean section, a comparison of hospital and home delivery, a study of the midwife and an analysis of the patient's economic status.

Specifically, regarding the three great causes of puerperal deaths, it is shown that for septicemia 75 % were judged to be preventable; of these, the physician was held responsible for 81%. In the hemorrhage group, 76% were judged to be preventable; of these, the physician was held responsible for 76%. In the albuminuria and eclampsia group, 72% were judged to be preventable. Of these, the patient was held responsible in 69%. The conclusions and recommendations merit the serious consideration of all who are concerned in the problem of public health and, especially, maternal welfare. There can be little doubt that the final statement would apply to any large city in the United States. "The hazards of childbirth in New York City are greater than they need be. Responsibility for reducing them rests with the medical profession." What does the profession propose to do about it?

P. W.

## BOOKS RECEIVED.

### NEW BOOKS.

*Life of Christian Samuel Hahnemann, Founder of Homoeopathy.* By ROSA WAUGH HOBHOUSE. With a Preface by SIR JOHN WEIR, K.C.V.O., M.B. Pp. 288; illustrated. London: The C. W. Daniel Company, 1933. Price, 7/6.

*Medicine in Virginia in the Nineteenth Century.* By WYNDHAM B. BLANTON, M.D. Pp. 466; illustrated. Richmond, Va.: Garrett & Massie, Inc., 1933. Price, \$7.50.

*Wilhelm Conrad Röntgen and the Early History of the Roentgen Rays.* By OTTO GLASSER, Cleveland Clinic Foundation. With a Chapter "Personal Reminiscences of W. C. Röntgen" by MARGRET BOVERI, Berlin. Pp. 494; 96 illustrations. Springfield, Ill.: Charles C Thomas, 1934. Price, \$6.00.

*Birth Control in Practice.* Prepared Under the Supervision of a Scientific Advisory Committee. Text and Tables by MARIE E. KOPP, Ph.D., with a Foreword by ADOLF MEYER, M.D. Pp. 290; 50 tables. New York: Robert M. McBride & Co., 1934. Price, \$3.75.

*de Venarum Ostiolis 1603 of Hieronymus Fabricii.* Facsimile Edition with Introduction, by K. J. FRANKLIN, D.M., Tutor and Lecturer in Physiology of Oriel College and University Demonstrator of Pharmacology, Oxford. Pp. 98; illustrated. Springfield, Ill.: Charles C Thomas, 1933. Price, \$3.00. (Review p. 414.)

*Benign Tumors in the Third Ventricle of the Brain: Diagnosis and Treatment.* By WALTER E. DANDY, M.D., Adjunct Professor of Surgery, The Johns Hopkins University. Pp. 171; 120 illustrations. Springfield, Ill.: Charles C Thomas, 1933. Price, \$5.00.

*The Surgical Clinics of North America, Vol. 13, No. 6 Index Number (Pacific Coast Surgical Association Number—December, 1933).* Pp. 284; 97 illustrations. Philadelphia: W. B. Saunders Company, 1933.

*Recent Advances in Endocrinology.* By A. T. CAMERON, M.A., D.Sc. (Edin.), F.I.C., F.R.S.C., Professor of Bio-chemistry, Faculty of Medicine, University of Manitoba; Biochemist, Winnipeg General Hospital. Pp. 365; 54 illustrations, including 2 plates. Philadelphia: P. Blakiston's Son & Co., Inc., 1934. Price, \$3.50.

- Bacteriology for Medical Students and Practitioners.* By A. D. GARDNER, D.M., F.R.C.S., Fellow of University College, Oxford Member of Research Staff, Medical Research Council. Pp. 276; 31 illustrations, 27 tables. New York: Oxford University Press, 1933. Price, \$2.25.
- The Modern Treatment of Syphilis.* By JOSEPH EARLE MOORE, M.D., Associate in Medicine, The Johns Hopkins University; Physician-in-Charge Syphilis Division of the Medical Clinic and Assistant Visiting Physician, The Johns Hopkins Hospital. Pp. 535; illustrated. Springfield, Ill.: Charles C Thomas, 1933. Price, \$5.00.
- The Teaching of Preventive Medicine in Europe.* (University of London Heath Clark Lectures, 1932, delivered at The London School of Hygiene and Tropical Medicine.) By CARL PRAUSNITZ, M.D. (BRESLAU), M.R.C.S. (ENG.), L.R.C.P. (LOND.), Professor of Hygiene in the University of Breslau. Pp. 180; 37 illustrations. New York: Oxford University Press, 1933.
- America Self-contained.* By SAMUEL CROWTHER. Pp. 340. Garden City, N. Y.: Doubleday, Doran & Co., Inc., 1933.
- Mental Hygiene in the Community.* By CLARA BASSETT, Consultant in Psychiatric Social Work, Division on Community Clinics, The National Committee for Mental Hygiene, etc. Pp. 394; 1 illustration. New York: The Macmillan Company, 1934. Price, \$3.50.
- Neurology.* By ROY R. GRINKER, Associate Professor of Neurology, The University of Chicago. Pp. 979; 401 illustrations. Springfield, Ill.: Charles C Thomas, 1934. Price, \$8.50. (Review p. 415)
- Treatment of the Commoner Diseases.* By LEWELLYS F. BARKER, M.D., Professor Emeritus of Medicine, Johns Hopkins University; Visiting Physician, Johns Hopkins Hospital, Baltimore. Pp. 319. Philadelphia: J. B. Lippincott Company, 1934. Price, \$3.00.
- Photochemical Immunization.* By S. PESKIND, B.S., M.D. Pp. 73. Cleveland: S. P. Mount Company, 1933. Price, \$1.00.
- The Lyophilic Colloids.* (Their Theory and Practice.) By MARTIN H. FISCHER, Professor of Physiology in the University of Cincinnati, and MARIAN O. HOOKER, Research Associate in Physiology in the University of Cincinnati. Pp. 246; 84 illustrations. Springfield, Ill.: Charles C Thomas, 1933. Price, \$4.50.

## NEW EDITIONS.

- Notes on the Medical Treatment of Disease.* By ROBERT DAWSON RUDOLF, C.B.E., M.D. (EDIN.), F.R.C.P., Professor of Therapeutics in the University of Toronto, Consulting Physician, Toronto General Hospital and Victoria Hospital for Sick Children, Toronto, etc. Pp. 540. Fourth edition. Toronto: The University of Toronto Press, 1934. Price, \$4.00.
- Bacterial Infection.* By J. L. T. APPLETON, JR., B.S., D.D.S., Professor of Microbiology and Bacteriopathology, The Thomas W. Evans Museum and Dental Institute School of Dentistry, University of Pennsylvania. Pp. 654; 122 illustrations, 4 colored plates. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1933. Price, \$7.00.

# PROGRESS OF MEDICAL SCIENCE

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## **PATHOLOGY AND BACTERIOLOGY**

UNDER THE CHARGE OF

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### **STUDIES ON HEMOLYTIC STREPTOCOCCI.**

THE importance of hemolytic streptococci in human and animal infections is reflected in the literature in that, even for 1 year the number of reports on these microorganisms forbids adequate analysis in any relatively limited review. OKELL (*Lancet*, 1932, 1, 761, 815, 867), in an extensive survey, clearly indicated a number of the outstanding problems and gave his reasons for believing in the essential unity of the human hemolytic streptococci. Methods of fermentation or agglutination had not been found of value in differentiating species within the group. The position of *S. "epidemicus"* and certain hemolytic streptococci of animal origin had not yet, however, been clearly defined. He considered three properties of the human hemolytic streptococci as characteristic of their pathogenicity under the headings: 1. Production of an erythrogenic (or rash producing) toxin immunologically identical for all strains and which is neutralized by "scarlatinal antitoxin." 2. A pyogenic property perhaps related to streptococcal hemolysin to which there is no effective antibody. 3. An invasive property which may or may not be linked with the pyogenic property and to which antibodies, to particular strains only, are available. These elements in the development of infections vary in intensity from case to case and this variation, together with that in the host's defense, accounts in his opinion for the different pathologic and clinical patterns of human streptococcal disease. The allergic conception of scarlet fever he considered had little to recommend it.

The survey of some of the recent (1933) contributions to our knowledge must perforce be short but will be based chiefly on further developments since Okell's analytical paper. The further attempts to differentiate hemolytic streptococci of human origin into groups which could be correlated in any useful way with types of human disease or localization of the infective process have not been very successful. EDWARDS (*J. Bacteriol.*, 1933, 25, 527), however, continuing his earlier studies, was able to distinguish hemolytic streptococci of human from

those of animal origin in 96%, using 173 of animal (chiefly equine) and 75 of human origin. He felt nevertheless that a final separation of human and animal strains has not yet been effected. The human strains as a rule fermented trehalose but not sorbitol and gave a pH value in glucose broth of 5.8, while animal strains produced acid in sorbitol and only rarely in trehalose with a pH value in glucose broth of 5 to 5.2. The presence of capsules on the majority (159 Type A) of animal strains and their frequent mucoid colonies make them indistinguishable from *S. epidemicus* and Edwards is of the opinion that these animal strains are not the causative agents of septic sore throat. A small group (8 *S. equi*) failed to ferment either sorbitol or trehalose and also produced no acid from lactose. This failure of *S. equi* to ferment lactose was also emphasized by HAUPT (*Centralbl. f. Bacteriol., Orig.*, 128, 110, 1933). LANCEFIELD (*J. Exp. Med.*, 1933, 57, 571) has gone further in a study of 106 strains of hemolytic streptococci from man, other animals, milk and cheese. These included a number of Edwards' strains and other carefully studied cultures from many laboratories. She used precipitin tests with hot hydrochloric acid extracts of the bacteria as antigens and the sera of rabbits immunized with formalinized cultures and was able to classify all but two of the strains into five distinct groups. Group A (23) strains were chiefly human; B (21) high acid producing sodium hippurate-hydrolyzing varieties from bovine and dairy sources; C (49) from a variety of animal sources including those strains of bovine origin which attained a final pH of about 4.8 and did not hydrolyze sodium hippurate; D (8) from cheese only; E (3) from certified milk. She found a striking correlation between her serologic methods and the biochemical and cultural reactions and gave tables showing the results of the reduction of methylene blue milk, growth on 10 and 40% bile agar, fermentation of trehalose and sorbitol and lysis with a streptococcus bacteriophage from sewage, in addition to the tests mentioned above. The specificity of the precipitin reaction was probably, she thought, dependent upon chemically related but serologically specific substances—the group specific substance in the human strains, Group A being of carbohydrate nature as was also that in Group B, and in the other groups this had not been determined. Agglutination would not appear to be as satisfactory for many reasons. MUELLER and KLISE (*J. Infec. Dis.*, 1933, 52, 139) used it in a classification of 225 hemolytic streptococci of scarlet fever, and found two-thirds of these fell into six well defined groups which were seldom found in normal throats not in relation to streptococcal disease. These authors considered agglutinability as a reasonably constant attribute of hemolytic streptococci.

Not many new technical methods for growing hemolytic streptococci from patients have appeared during the last year. ALIVISATOS (*Centralbl. f. Bakteriolog., Orig.*, 1933, 129, 111), in a study of blood cultures in cases of puerperal sepsis, believed the bactericidal activity of the blood was the greatest cause of failure. He advocated the use of 20 cc. of citrated blood, which he divided into two lots, one of which was added at once to 100 cc. of 1.5% dextrose bouillon (Method A), the other was centrifuged 12 to 15 minutes, all but about 1 cc. of the supernatant fluid was carefully withdrawn and the remainder seeded as above (Method B). The latter method (B) gave positive cultures 36% more often than the former method (A). ROBINSON (*Am. J. Surg.*,



1933, 20, 131), in a paper on the revaluation of prevailing theories and principles of puerperal infections, pointed out that pathogenic bacteria do not ordinarily multiply in the blood stream of human beings but in the septic focus from which they enter the lymph and blood streams at intervals. The failure to recover bacteria from the blood in outspoken cases of bacteremia he believed due to taking the blood during or just after the chill rather than 3 to 5 hrs. before its occurrence and to the neglect of making anaërobic cultures. The identification of hemolytic streptococci in cultures from maternity cases has been considered, as a rule, relatively easy, but FRY (*J. Pathol. and Bacteriol.*, 1933, 37, 337) refers to a number of cases from which he was able to isolate typical Beta hemolytic streptococci from the blood or uterus, while from other foci in the same persons strains were recovered which only gave green discoloration on horse blood agar when grown aërobically and which gave no green but a marked Beta hemolysis under anaërobic conditions, and these formed soluble hemolysin in horse serum broth. He also found a number of other interesting variant strains. The possibility that mixed cultures accounted for his results was considered and discarded. The author advocated using anaërobic plates or digging into the blood agar in all primary cultures in order to avoid missing such strains. The importance of anaërobic streptococci is well recognized, but since it is rare for these strict anaërobic strains to produce hemolysis they will not be discussed in any detail in this survey. COLEBROOK and HARE (*J. Obst. and Gynec. Brit. Empire*, 1933 40, 609), reported on their association with puerperal fever, in which they considered them next in importance to the aërobic hemolytic streptococci. He found only 2 strains out of some 60 studied which gave hemolysis on the surface of blood agar plates anaërobically.

The problem of dissociation of hemolytic streptococci is especially important, as it concerns the diagnosis of the strains at the time of isolation. It is too complicated a subject to deal with here in any profitable way. SPASSKY (*Centralbl. f. Bakteriöl., Orig.*, 1933, 128, 251) has described and illustrated dissociation forms of laboratory strains of scarlet fever streptococci in which the changes were associated with the development of daughter colonies about the normal smooth colony, or the phenomenon of lysis of the colonies. The direction of change was always from S to R, the reverse never being observed. The R form no longer caused hemolysis with various kinds of blood, was biochemically less active, produced no toxin and the morphology became like that of the diphtheroid bacilli. On the other hand, PILOT and STOCKER (*Proc. Soc. Exp. Biol. and Med.*, 1933, 31, 181) reported a non-hemolytic variant of a scarlet fever strain originally obtained from the infected udder of a cow, the milk of which had been held responsible for an epidemic of scarlet fever and which retained its property of producing toxin specific for scarlet fever. At first this strain resembled *S. epidemicus* with mucoid colonies and capsules and it, with another similar strain obtained from a sporadic case of scarlet fever, was studied by PILOT and DAVIS (*J. Infec. Dis.*, 1933, 53, 29) and differentiated to their satisfaction from *S. epidemicus* by toxin neutralization tests. The toxins of these mucoid scarlet fever strains corresponded to the scarlet fever and not to the *S. epidemicus* toxin. They refer to having recently isolated, from cases of erysipelas, hemolytic streptococci which resembled the above mucoid types and suggested that all these may represent

variation or mutation forms and that they may be more virulent than the "normal" form.

The interrelationships between the strains of hemolytic streptococci from scarlet fever, erysipelas and puerperal fever have received perhaps most attention, and the property of producing erythrogenic toxins has been used both to prove and to disprove the unitarian interpretation. WADSWORTH (*Canad. Pub. Health J.*, 1933, 24, 1), said: "The etiological relationship of the streptococci to puerperal fever, septic sore throat and erysipelas is no longer questioned, but claims identifying a specific streptococcus as the incitant have been practically abandoned. Traditional conceptions of scarlet fever as a specific disease must give way if the streptococcus is to be accepted as the incitant. Scarlet fever and erysipelas are now in practically the same category, that is, must be regarded simply as different manifestations of streptococcus infection developing under special conditions of tissue susceptibility, since there is no known method of distinguishing between the so-called *S. scarlatinae* and the *S. erysipelatus*." After studying the toxins of at least 1000 strains of hemolytic streptococci and attempting to group them according to the reactions of the tissues of different animal species to the toxins and also by the extent to which they are neutralized by immune sera or antitoxins, he concluded that no one group was associated specifically with any particular symptom complex but quite the contrary, so that representatives of the several groups were found in the different diseases incited by the streptococci.

All this suggested to him "that subtle conditions of tissue susceptibility underlie the mechanisms of these reactions." Virulence is not necessarily related to toxin production and there are many other unsolved problems for the future. The important practical point is that therapeutic serum should be potent and of wide valency. The demonstration of TRASK and BLAKE (*J. Am. Med. Assn.*, 1933, 101, 753) of a toxin from 3 severe cases of scarlet fever in which potent scarlatinal antitoxin was ineffectual, confirmed the earlier views on the heterogeneity of toxins and antitoxins in man, and it is significant that Wadsworth has prepared a polyvalent antitoxin which includes this new toxin, the standard Dick toxin, and many others in its range of neutralization.

There are many difficulties in the interpretation of the skin tests, difficulties associated with titration, neutralization by antitoxin and individual differences in the reactions of human and animal subjects. KRESTOWNIKOWA and RJACHINA (*Ztschr. f. Immunitätsforsch. u. exp. Therap.*, 1933, 78, 414) compared the purified toxins prepared from the Dochez strain of the scarlet fever streptococcus (having found this strain a stronger toxin producer than the Dick 8 strain) and from the Birkhaug strain of the erysipelas streptococcus. The preparations were freed from protein, and then purified by a series of dialyses, alcoholic precipitations and dryings to a constant weight with yellowish, rather hygroscopic powders as the products. These materials were susceptible to oxidation, contained a reducing substance set free after acid hydrolysis, had part of the nitrogen in the form of aminonitrogen, showed a free carboxyl group and were levorotatory. The scarlet fever and erysipelas toxins thus purified showed chemical differences, the aminonitrogen being lower, the angle of rotation being less, and the reducing substance being more easily destroyed in the erysipelas than in the scarlet fever preparations, but as the purification was made more

perfect the two substances became more alike. The two purified toxins in immunity reactions with specific sera (precipitin reactions with convalescent and animal antisera being particularly clear cut) complement binding and neutralization tests showed the two substances to be very similar if not identical. The toxic characteristics were always more marked with the scarlet fever than with the erysipelas substance, the latter, however, always produced severe cramps in rabbits which the former did not do. They considered the problem of identification as still unsettled.

The differences between the toxicogenic powers of different strains of streptococci from scarlet fever, erysipelas or other infections make one hesitate to lay too much stress on relatively slight qualitative differences until the essential criteria have been more clearly enunciated. The complete story of the infections by the hemolytic streptococci cannot be completed without supplementing our knowledge concerning the erythrogenic toxin with that of other offensive weapons of the streptococci and a more careful clinical study of the patients, subject to such infections, regarding the nature of their response to the streptococcus antigens. DAY (*J. Pathol. and Bacteriol.*, 1933, 37, 169) reported his experience with an antigen which was obtained from virulent cultures of streptococci both hemolytic and non-hemolytic and which he called V antigen. This antigen, quantitatively related to virulence, was type specific and was obtained by the use of  $\frac{N}{10}$  hydrochloric acid at 60° C. There was evidence that it protects the bacteria from phagocytosis. It was formed during active growth, was attached to the cocci, was resistant to acid, was destroyed by alkali and heat and bacterial enzymes and was readily adsorbed to protein. It was antigenic and excited active immunity while the sera of immunized animals gave a passive immunity. It was suggested that the substance is of the nature of a protective secretion attached to the cocci.

Considerable advance has been made in our knowledge of hemolysin. TODD (*J. Pathol. and Bacteriol.*, 1933, 36, 435) found the addition of serum to broth permitted the production of a streptolysin by the cocci which had characteristics distinctive from that produced in broth without serum. The two are equally hemolytic and both are antigenic. The hemolysin formed in serum-free broth is so sensitive to oxidation that reducing agents must be used to demonstrate its total content, it is easily adsorbed by filters and readily combines with its specific antibody. The lysin produced in serum broth is more stable, relatively resistant to oxidation and reduction, resists adsorption and combines very little with its antibody. He believed the reason hemolysis does not occur *in vivo* is because the serum-hemolysin is neutralized by lecithin (Gordon and Stansfield, 1929). TODD, LAURENT and HILL (*J. Pathol. and Bacteriol.*, 1933, 36, 201) studied the relationship between streptococcal antitoxin and antistreptolysin, and showed they were distinct and separate antibodies. SWIFT and HODGE (*Proc. Soc. Exp. Biol. and Med.*, 1933, 30, 1022), by adding filtered salts, buffers and glucose to beef-heart peptone broth previously sterilized at 100° C., obtained a medium which gave extremely heavy bacterial growths and a good yield of streptolysin. HODGE and SWIFT (*J. Exp. Med.*, 1933, 58, 277), considerably improved the method for titrating antistreptolysin by showing that streptolysin might have varying hemolytic but constant combining capacity. It being the reduced streptolysin which

exhibits hemolytic activity, they used sodium hydrosulfite as a reducing agent and noted that the yield of hemolytic streptolysin continued to increase for 24 hrs. *in vacuo*, but that it was impossible to reduce all the hemolysin so as to give a constant hemolytic titer corresponding to the combining power, suggesting that a part of the hemolysin may have been altered to an irreversible form. However, it could be reduced, remained stable for months if stored in the ice-box under vaseline and could be used as a standard in titrating antistreptolysins.

The varying sensitivity of the tissues to streptococci both hemolytic and non-hemolytic and to their products has received considerable attention. BÖHMIG and SWIFT (*Arch. Path.*, 1933, 15, 611) noted that rabbits, after prolonged intravenous inoculation with streptococci became hypoergic or immune, but if inoculated intracutaneously they became hypersensitive. They showed that there was a definite relationship between hemolytic streptococci and *S. viridans* in these tissue responses in the skin to a later intracutaneous inoculation. Rabbits made hypersensitive to green streptococci were one hundred times more responsive, as determined by size of the lesion, to homologous streptococci and showed more marked edema, tissue destruction, abscesses, capillary endothelial swelling and more marked monocyte infiltration than did normal or immunized animals. The response to whole microorganisms, they emphasized, was different from that to one or more of its components. MCGIBBON (*Lancet*, 1933, 2, 1363) used an extract free from soluble toxin—a “nucleoprotein endotoxin”—and tested the cutaneous reactions in cases of scarlet fever and erysipelas. Because of the development of these reactions during convalescence they were considered of allergic nature. In cases in which the Dick test tended to remain positive, allergy was slow in appearing. The reaction in erysipelas was not so well marked as in scarlet fever, but it was more like erysipelas itself; there was, however, no actual pain, nor did blebs develop. SEEGAL, HEIDELBERGER, JOST and LITTLE (*Proc. Soc. Exp. Biol. and Med.*, 1933, 30, 582) used the precipitin test with 172 sera of well persons and 138 from those with various diseases—*S. viridans* endocarditis, rheumatoid arthritis, hemolytic streptococcus diseases, acute, subacute and healed glomerular nephritis and cases of peptic ulcer. Two protein fractions and the group carbohydrate of *S. hemolyticus* and the nucleoprotein of *S. viridans* served as antigens. There was little or no precipitin in the normal group to any of the fractions. In the cases of subacute *S. viridans* endocarditis or rheumatoid arthritis there was strong precipitin formation against the hemolytic streptococcus protein antigens, which was moderate in the hemolytic streptococcus diseases, acute and subacute glomerular nephritis, and peptic ulcer. The reactions to hemolytic streptococcus carbohydrate was strongest in the hemolytic streptococcus infections or rheumatoid arthritis. The endocarditis cases alone gave marked precipitin formation against *S. viridans* protein. There are many valuable facts in this report, but their correct interpretation must await fuller knowledge of the factors concerned.

HOOKE (J. *Immunol.*, 1933, 24, 65) did not consider the arguments in favor of the allergic interpretation of scarlet fever, nor the objections to the toxin-antitoxin hypothesis, to be well founded. He looked upon cutaneous allergy as a local expression of an enhanced capacity for an unusually rapid development of specific resistance. He further cited

the evidence which shows that allergic inflammation delays bacterial invasion and hastens healing.

The unsettled differences of opinion regarding the relationship of hemolytic streptococci to acute rheumatism and rheumatoid arthritis must be left for another review.

The discovery of the fibrinolytic action of hemolytic streptococci by TILLET and GARNER (*J. Exp. Med.*, 1933, 58, 485) seems full of promise as a help in making clearer the interpretation of many streptococcus diseases. The fibrinolytic capacity of hemolytic streptococci would appear to be an important offensive weapon of these microorganisms in their attack on the body. The active principle was filtrable and acted apparently only on normal human fibrin clot, which may serve as still another method of differentiating human from animal strains. It was extremely active requiring, as a rule, about 2 to 10 min. completely to dissolve the clot. *S. viridans* strains were inactive, as were some 30 other bacterial species. The plasma of patients recovered from acute hemolytic streptococcus infections they found to be highly resistant to fibrinolysis, and also that it can convey to normal plasma clot the same antifibrinolytic property. Rabbit fibrin clot was insusceptible to its action, but if human thrombin were used to produce the clot, fibrinolysis was no longer inhibited, which fact offers a means further to analyze the phenomenon. The presence of fibrin in the reaction zone at the primary focus of infection is usually considered as helping to prevent the entrance of streptococci into and along the lymphatics, so that, if this barrier is removed by the fibrinolytic agent, this may be another of the long sought factors which determine the invasive capacity of hemolytic streptococci.

The year's progress in the study of this important group of bacteria as indicated in this brief and incomplete review has been, we believe, very substantial and has opened many hopeful roads for future investigations.

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## HYGIENE AND PUBLIC HEALTH

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UNDER THE CHARGE OF

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## AMEBIC DYSENTERY.

AMEBIC dysentery generally has been regarded as a disease of warm climates, although it has been recognized as occasionally occurring elsewhere; indeed, a rather large number of cases has been reported from temperate climates. The recent outbreak, which had its origin in Chicago, shows that it is necessary to revise this and other conceptions of the disease generally held. New light also has been thrown on its mode of transmission. Hitherto the means of infection have

been rather obscure. Contaminated water and food have been incriminated as vectors, but without very conclusive positive evidence. Vegetables from southern sources have been accused. Convalescents or healthy carriers shedding ameba cysts have been suspected, but no very definite evidence has been brought forth to show that this mode of infection is important. The recent outbreak, which began in Chicago during the summer of 1933 and continued on into the autumn, had several features interesting from different points of view, notably from the epidemiologic and clinical aspects. The coincidence of the Century of Progress Exhibit and the paucity of early information on the subject added to the gravity of the situation. Approximately 800 cases throughout the country have been identified as having had their origin in Chicago, and the large majority of these has been traced to a single hotel. An intensive laboratory study of the food handlers in this hotel showed an extraordinarily high incidence of ameba carriers; and combined laboratory and clinical examinations demonstrated a number of active cases of the disease, though usually not with very pronounced symptoms. A study of the water supply and of the sewage disposal system of the hotel incriminated demonstrated the probability of sewage contamination of drinking water.

Clinically, the cases were not all of the typical textbook patterns, but they fell within the well-recognized deviations. These variations extended all of the way from mild abdominal discomfort with either diarrhea or constipation to rather severe manifestations with tenesmus, bloody and mucous stools, toxic symptoms and death. Many of the cases were mildly febrile and in a few the temperature was rather high for amebic dysentery.

Perhaps the most interesting clinical feature was the fact that a good many of the cases were mistaken for surgical conditions and even subjected to surgical intervention. The most common erroneous diagnosis from a surgical point of view was appendicitis; some cases were suspected of being cholecystitis; and a smaller number were regarded as possibly malignant in nature. Perhaps the commonest error was to regard cases as non-specific "colitis" or "ulcerative colitis." The mortality was high in the cases subjected to operative procedures. The high incidence of erroneous diagnoses demonstrated in this outbreak prompts one to suspect that isolated cases not associated with a general outbreak may also often pass under incorrect diagnoses.

The incubation period, which could be fairly accurately established in many cases, usually has varied from a week to 3 months, with the majority of patients falling ill within 3 or 4 weeks after exposure.

The onset may be rather sudden and stormy, or may be manifested only by vague abdominal distress. Stools may vary from those normal or practically so to those made up largely of mucus and blood; or there may be only an increase in the number of stools. The Roentgen ray findings may be suggestive of other conditions. Under appropriate treatment the symptoms usually clear up rapidly, but if the condition is not recognized promptly it may become chronic or recurrent.

The case mortality in the present outbreak has been around 5%.

The laboratory aspects of the cases are interesting. A blood count does not give much assistance in eliminating surgical conditions, since a leukocytosis is not rare. The detection of amebas in the stool is of aid in diagnosis. In acute cases the motile protozoa containing red

blood cells offer little possibility of confusion with other organisms. The cystic stage, however, which is the common phase in the life cycle found in the carrier, is not so readily differentiated from non-pathogenic amebas—indeed, it is perhaps not an exaggeration to say that only an expert protozoologist, or a technician who has been thoroughly trained by an expert, should attempt this differentiation. In some cases, material secured by proctoscopic examination may show organisms that would have been missed otherwise.

Repeated stool examinations may be necessary in clinical cases and in carriers without manifest symptoms. A single negative examination is to be given but little weight, and even repeated examinations may give misleading negative results. Perhaps one would be warranted in saying that, in the presence of tenesmus associated with blood and mucus in the stools, clinical manifestations should be given greater weight than negative laboratory findings. On the other hand, the presence of amebas, particularly the encysted form, does not necessarily prove that the clinical condition present is due to amebas. Serologic methods of diagnosis have not been sufficiently worked out to be applied clinically, and the same may be said of the cultivation of the amebas. It is well known that a considerable percentage of the general population of this country (some authorities say from 5 to 10%) harbors amebas, and it will readily be perceived that in any considerable group of cases of any disease some ameba carriers will be found whose clinical conditions might in no wise be related to the presence of the parasites.

There have been material advances in the treatment of this disease within comparatively recent years. For the relief of symptoms of acute amebiasis, including hepatitis, the use of emetin in doses of 1 mg. per kilo daily, over a period not exceeding 10 days, appears to give the best results. Care must be taken in the use of the drug since it is highly toxic, and an interval of at least 10 days should elapse between series of injections.

In the treatment of the carrier condition, most satisfactory results have been obtained with some of the later drugs, such as chiniofon (0.25 to 1 gm., by mouth, thrice daily) or earbarsone (0.25 gm., twice daily).

In the present outbreak, cases have been predominantly in adults, and largely among those of the more comfortably situated group from the economic point of view.

It has been recognized that amebas are likely to become widely distributed in families once the infection is implanted in a member of the family group. It is too early to say whether secondary foci are likely to develop as a sequel to the Chicago outbreak. We are still in ignorance of many factors governing transmission.

Two explanations have been advanced to account for the sharp outbreak forming the basis of this discussion: (a) That a strain of *Endamoeba histolytica* of unusual virulence was imported or developed among food handlers in Chicago, or (b) that a bacterial organism living in symbiotic relation with the amebas accounted for the high virulence of the strain and possibly for some of the symptoms. Whether either of these considerations is important cannot be stated at present.

From the purely public health point of view, theoretically, prophylaxis should be very simple. The necessity for remedying conditions lead-

ing to possible contamination of a water supply is obvious. The examination of food handlers occurs at once as the logical procedure when epidemiological evidence points to this source of infection, but practically this is not so easy. The number of examinations required before an individual is to be considered negative multiplies the work very materially. In practice, so large a number of food handlers are found infected that their hospitalization and treatment assume proportions too large to be dealt with ordinarily in a satisfactory manner. In addition, there are few technicians sufficiently well qualified to render dependable opinions on intestinal protozoa. It has been estimated that a skillful, capable and experienced technician can examine only 8 to 10 specimens a day, and as the number of food handlers in any city may run as high as 5% of the population, the time required and the work involved obviously make it a difficult, or impossible, procedure. The problem is further complicated by the well-known fact that carriers may be found free of recognizable amebas in stool specimens for long periods, only to have them reappear at later examinations. A food handler who was known to be an ameba carrier in 1927 was found to be involved in the most recent outbreak, though there had been a number of negative stool examinations in the interval. It is the carrier rather than the clinical case who spreads the infection. On the whole, therefore, the examination of food handlers appears to be impracticable.

It is interesting to note that in the present outbreak, flies have not been mentioned as an agency of transmission. This suggests that they may be much less important than had been thought by many.

A mode of attack on the problem of transmission is through improvement in sanitary conditions surrounding food handlers, such as installing adequate toilet and washroom facilities and taking measures to require personal cleanliness on the part of food handlers. These means do not seem to have been altogether successful in Chicago, probably because contamination of the water supply, which was not recognized early, seems to have been the most important factor in the outbreak. There are stumbling blocks which are not to be ignored. Perhaps the chief obstacle lies in the difficulty in creating a sustained effective interest on the part of any group in careful systematic cleansing of the hands after a visit to the toilet. Probably few persons could be sufficiently convinced that they are a source of danger to others to impel them to take the measures (such as hand scrubbing or the wearing of gloves) that would be necessary to protect others.

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## PHYSIOLOGY

PROCEEDINGS OF  
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF JANUARY 15, 1934.

**The Changes in Total Content and Osmolal Concentration of Glucose and Chlorid After the Ingestion of Glucose by Diabetic Patients.**—F. WILLIAM SUNDERMAN and E. S. WILLIAMS (Laboratory of Research Medicine, University of Pennsylvania). After the ingestion of glucose by diabetic patients the concentration of glucose in serum was increased and the concentrations of total fixed base and of chlorid were decreased. When calculations were made which permitted an estimation of the change in the total content of these components in the serum, it was found that the amounts of glucose, chlorid, and water of the serum were all increased after the administration of glucose.

The experiments suggest that glucose entering the serum following glucose ingestion tends to draw water from the tissues. The water added to the serum with the glucose and from the tissues dilutes the serum electrolytes and sets up a potential gradient for electrolyte from tissue to serum, resulting in an inflow of chlorid. As the glucose is built up into glycogen or otherwise removed the potential gradient will tend in time to be reversed and electrolyte will pass from serum to tissues. The experiments illustrate the fact that a potential gradient induced with respect to a single component induces a gradient with respect to all the other components and sets them moving in one or the other direction.

**The Spectral Sensitivity of Single Visual Sense Cells.**—H. K. HARTLINE (Eldridge R. Johnson Foundation, University of Pennsylvania). The effect of various wave-lengths of visible light in the stimulation of single visual sense cells has been studied by Dr. C. H. Graham and myself, employing the single-fiber preparation from the eye and optic nerve of *Limulus*. Oscillographic records were made of the discharge of impulses in a single optic nerve fiber, in response to stimulation of the attached sense cell by light from different regions of the visible spectrum. Wratten Monochromatic Filters supplied the spectral lights, the total intensity transmitted by each filter being determined by means of a thermopile.

The response of the single visual sense cell does not vary qualitatively with wave-length of stimulating light; by properly adjusting the intensity, responses can be obtained which are identical, impulse for impulse, for all the spectral lights used. The reciprocals of these intensities necessary to produce a constant response, plotted against wave-length, give the visibility curve of the single sense cell. This curve is symmetrical about a maximum at approximately 520  $\mu$ , falling off to low values in the red and in the violet. It closely resembles the visibility curve of human rod vision, with the maximum somewhat displaced.

Bundles from the optic nerve, containing several active fibers whose impulses can be distinguished by differences in size and shape, were used to determine whether there is any differential sensitivity among

the sense cells of the same eye, in different regions of the spectrum. Such a differential sensitivity has been found to exist in the eye of *Limulus*, and may be considered a peripheral mechanism of color vision.

**Studies on the Heart and Circulation in Disease; Estimations of Basal Cardiac Output, Metabolism, Heart Size, and Blood Pressure in 235 Subjects.**—ISAAC STARR, JR., J. S. DONAL, A. MARGOLIES, R. SHAW, L. H. COLLINS and C. J. GAMBLE (Laboratory of Pharmacology, and the Medical Division of the University Hospital, University of Pennsylvania). This study was made possible by the development of the katharometer method for the analysis of ethyl iodid by Donal and Gamble. This improvement so greatly increased the rapidity with which cardiac output could be estimated that over 500 determinations have been made on 235 subjects. These included 31 healthy persons and 204 patients from the wards of the University Hospital. The data contain groups of patients with intercurrent disease not affecting the circulation, with anemia, hypertension, hyperthyroidism, and neurocirculatory asthenia, also a few cases of Addison's disease, myxedema, and arteriovenous communications. Cases of various types of heart disease were studied also, *e. g.*, patients who had once been decompensated, cases of valvular disease, of arrhythmia, of coronary occlusion, of angina pectoris, and of aneurysm. On the other hand patients with acute cardiac decompensation, with advanced pulmonary disease, or with fever, were not studied.

The results have been subjected to statistical analysis. By this means the relationship of the cardiac output to age, sex, body surface, body weight, and heart size has been studied. The normal limits of cardiac output, heart work, stroke volume and arteriovenous oxygen difference have been defined, and the deviations in disease noted. These values give information concerning the circulation, but throw little light on the condition of the heart.

The most promising method of detecting myocardial disease is by the relationship of heart work per beat to heart size, an extension of Starling's "Law of the Heart," to clinical conditions. The normal limits of this relationship have been defined: healthy persons, patients with disease not affecting the circulation, and patients with disease of the circulation but with presumably normal hearts, give values within the normal range. But in patients with undoubted myocardial disease (who had once been decompensated) this relationship is abnormal almost without exception.

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**The Action of the Pyloric Sphincter.**—HARRY SHAY and J. GERSHON-COHEN (Gastro-intestinal Clinic of Jewish Hospital and Laboratory of Roentgenology, Graduate Hospital, Philadelphia). Our experiments have consisted of a roentgenologic study of gastric emptying and pyloric behavior in man following the gastric and duodenal application of various test substances. While many reagents were studied, this report is primarily concerned with the action of acid and alkali in 176 serial Roentgen examinations in 24 patients which indicate that:

1. Without due consideration to the individual gastric secretory response no proper evaluation of the experimental results could be made.
2. Of the three components concerned in gastric emptying, gastric peristalsis plays an incidental rôle only and is not concerned with pyloric

opening; gastric tonus is the greater motivating force, but the potency of each depends entirely upon the state of the pylorus.

3. When the stomach is empty, the normal state of the pylorus is that of relaxation. This is always seen in achlorhydries, but does not obtain in patients with free gastric acid.

4. The hydrochloric acid of the gastric contents is the natural intrinsic agent responsible for pyloric action. We do not imply, however, that it is the sole possible agent. Certain other ingested substances, such as various irritants, fats, hyper- or hypotonic solutions of sugars and neutral salts, through their chemical or physical action are equally efficacious.

5. Any agent (intrinsic or extrinsic) becomes effective in producing pyloric closure only upon reaching the duodenum. Here a reflex is activated and maintained until proper neutralization or dilution of the duodenal contents which makes it acceptable to the adjacent distal duodenum, has occurred. Then pyloric relaxation takes place.

6. The duodenal mucosa adjacent to the cap is most responsive to stimulation, though the response may be obtained in other portions as well. In general, the farther from the cap, the stronger the stimulus necessary to evoke the pyloric response.

7. Under normal conditions, the duodeno-pyloric reflex is not dependent upon duodenal filling.

8. Evidence is presented suggesting that the duodenal neutralizing mechanism is most highly developed in hyperchlorhydries and least in achlorhydries.

9. The antrum, pylorus, and duodenal cap appear physiologically to be intimately related.

Were we to picture our concept of pyloric action in a homely simile, as others have been wont to do, we would say that the stomach is like a dumbwaiter ever ready to deliver through its door, the pylorus, anything reaching it. The duodenum, however, sensitive connoisseur, is selective. If the gastric contents are acceptable to the official taster, the duodenal cap, gastric emptying continues uninterruptedly; if not, the door, the "pylorus," is hurriedly closed and stays so until the portion tasted, "Trial portion," is rendered acceptable.

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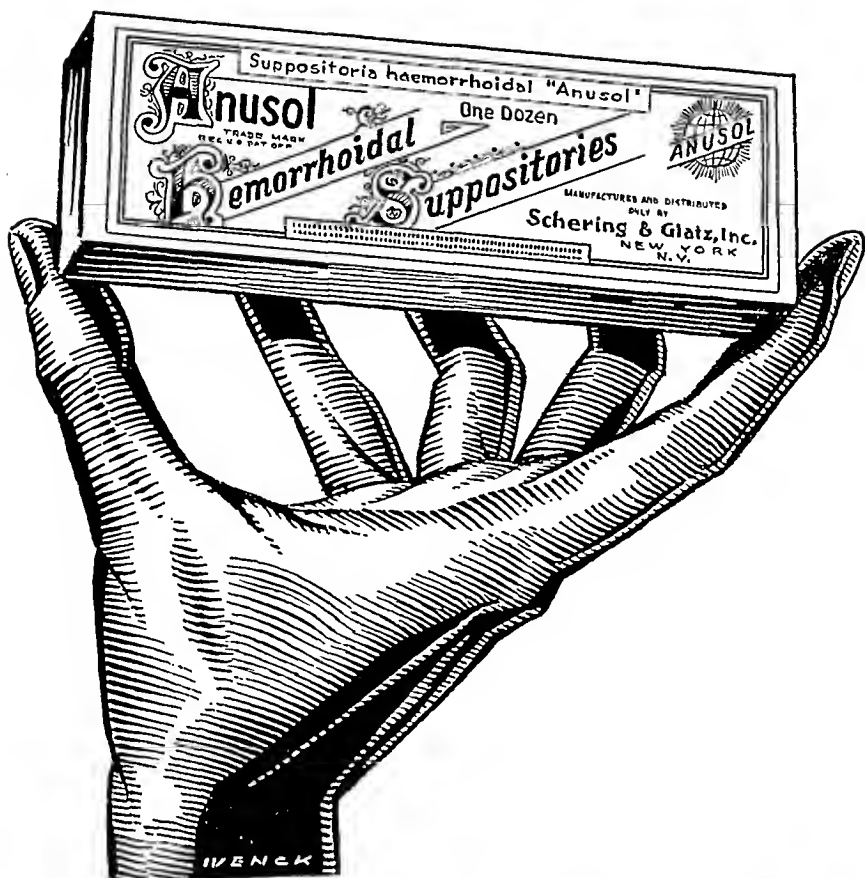
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By DR. ERICH GRAFE

Professor of Medicine and Director of the Clinic of Medicine and Neurology at the  
University of Würzburg, Germany

Translated by MARGARET GALT BOISE under the Supervision of

EUGENE F. DuBOIS, M.D. and HENRY B. RICHARDSON, M.D.

Medical Director, Russell Sage Institute of Path-  
ology; Professor of Medicine, Cornell Univer-  
sity Medical College, New York

Associate Professor of Medicine, Cornell  
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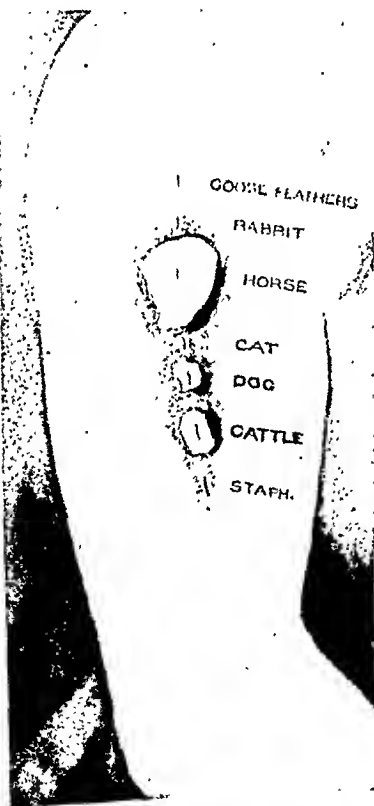
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WITH AN INTRODUCTION

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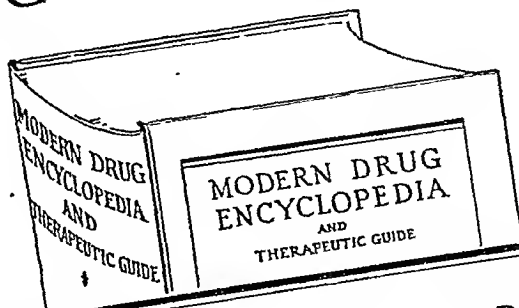
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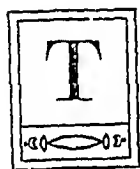
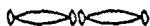
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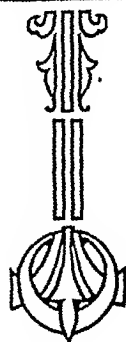
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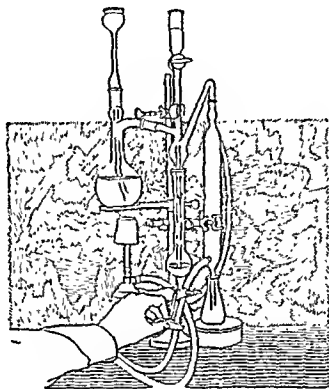
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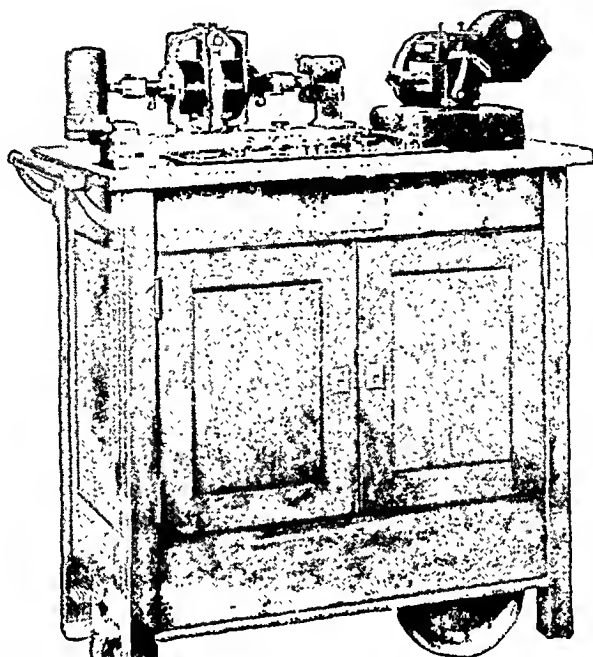
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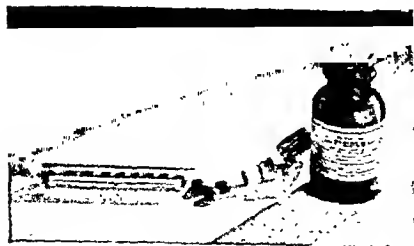
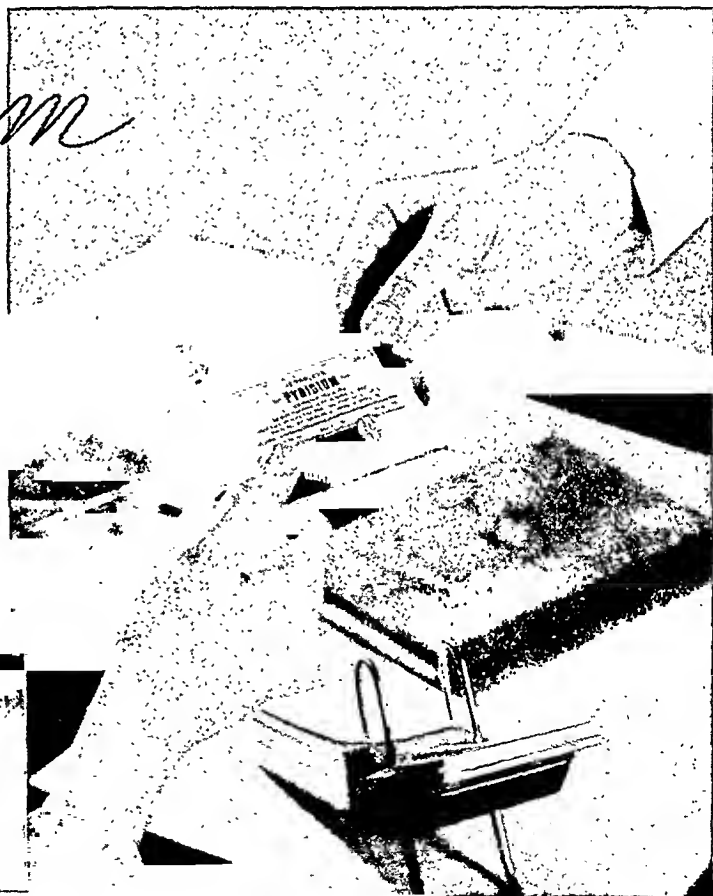
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In discussing the treatment of decomposition Feer says: "The period of repair may be shortened by giving suitable additional food; the best, probably, being buttermilk to which carefully regulated proportions of dextrin and maltose preparations or malt soup are added."—*E. Feer: Text-Book of Pediatrics*, J. B. Lippincott Co., Phila., 1922, p. 284.

In the treatment of infantile atrophy, Fischer recommends the following: "The carbohydrate should be increased by gradual addition of dextrimaltose.

"Malt soup or dextrimaltose (Mead's) should be added in teaspoonful or more doses to each feeding until the point of carbohydrate tolerance is reached."—*L. Fischer: Diseases of Infancy and Childhood*, F. A. Davis Co., Phila., 1925, V. 1, p. 285.

Grulee, discussing treatment of decomposition, observes: "As a rule it is best to start with 2 to 2½ or 3 ounces of albumin milk to the pound weight in 24 hours; the sugar to be added is in the form of a maltose-dextrin mixture. One should never delay too long in adding this."—*C. G. Grulee: Infant Feeding*, W. B. Saunders Co., Phila., 1922, p. 265.

Referring to the hypotrophic infant, Herrman writes: "In mild cases, the addition of dextrimaltose instead of cane or milk sugar may be sufficient to obtain a gain in weight."—*C. Herrman: The treatment of nutritional disorders in artificially-fed infants*, New York M. J. 114:158-160, August, 1921.

In discussing artificial feeding in athrepsia, Hess states: "The carbohydrates are usually added in a slowly fermentable form, such as the maltose and dextrin compounds, which are usually started by the addition of four grams per kilogram (1/15 ounce per pound) and increased until eight grams or more per kilogram (¼ ounce per pound) of body weight are added."—*J. H. Hess: Feeding and the Nutritional Disorders in Infancy and Childhood*, F. A. Davis Co., Phila., 1928, p. 278.

Concerning the treatment of marasmus, Hill says: "When the stools have become smooth and salve-like, carbohydrate, in the form of dextrimaltose, may be gradually added up to the limit of tolerance."—*L. W. Hill: Practical Infant Feeding*, W. P. Saunders Co., Phila., 1922, p. 281.

"... on bottle feeding should receive... of milk—a pint, or at the most 24 ounces in the 24 hours—to which cereal gruel and some form of sugar is added, preferably one of the malt dextrin preparations; also the early addition of other foods than milk to the baby's

diet."—*M. Jampolis: Infantile spasmophililia*, Interstate M. J. 25:652, Sept., 1918; *abst. Arch. Pediat.* 35:691, Nov. 1918.

With reference to the treatment of diarrhea, Lust writes: "After several days, 2% to 3% of a maltose-dextrin preparation may be added (Dextri-Maltose). This is preferable to the easily fermentable lactose or cane sugar."—*F. Lust: The Treatment of Children's Diseases*, J. P. Lippincott Co., Phila., 1930, p. 145.

"The treatment of artificially fed children in the first of these groups consists in putting them on a low fat dietary, and giving them carbohydrate in the form of one of the less fermentable sugars, such as dextrimaltose."—*L. G. Parsons: early infancy*, *Lancet*, 1:687-

Pearson and Wyllie in discussing the treatment of milder cases of marasmus say: "Regulation of this disturbed organismal balance is obtained by the addition of carbohydrates, while fat and casein are reduced. For this purpose dextrimaltose and flour are better than the ordinary sugars, since they are more slowly absorbed and have greater efficacy in their powers of controlling the flora in the large intestine."—*W. J. Pearson, and W. G. Wyllie: Recent Advances in Diseases of Children*, P. Blakiston's Son & Co., Phila., 1930, p. 116.

Regarding the treatment of the marantic infant, Raue states: "After the intolerance to sugar has been overcome a carbohydrate, preferably Dextri-maltose, may be added."—*C. S. Raue: Diseases of Children*, Boericke & Tafel, Phila., 1922, p. 427.

In discussing the treatment of atrophy, Thursfield and Paterson, state: "If the baby continues to improve, the next step in the treatment is to add to the milk one of the less fermentable carbohydrates, such as dextrimaltose;..."—*H. Thursfield, and D. Paterson: Diseases of Children*, William Wood & Co., 1929, p. 105.

"I also find dextrin-maltose an excellent addition to albumin-milk when the first object of that food has been achieved and a gain in weight is desired; in this way I have succeeded in feeding albumin-milk far beyond the period usually advised, with highly gratifying results."—*F. L. Wachenheim: Infant-Feeding; Its Principles and Practice*, Lea & Febiger, Phila., 1915, p. 158.

"Dextri-maltose has been substituted for lactose not infrequently, when the tolerance for the latter continues low."—*J. H. West: Low fat, high starch evaporated milk feeding for the marasmic baby*, *Arch. Pediat.* 48:189-193, March, 1931.

"Malt sugar is indicated when others fail to produce a sufficient gain, or when malassimilation of fat is evident."—*O. H. Wilson: The role of carbohydrates in infant feeding*, *Southern M. J.* 11:177, March, 1918; *abst. Arch. Pediat.* 35:447, July, 1918.

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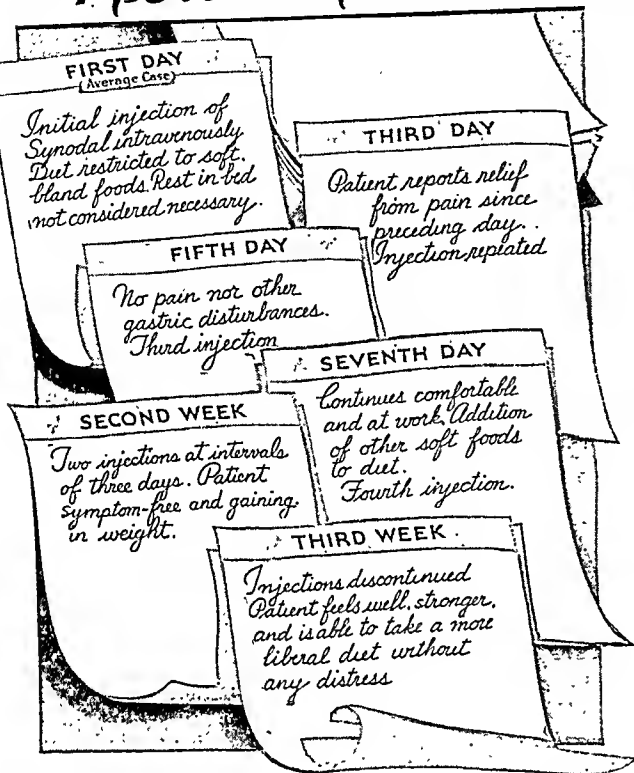
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Clinical Professor of Medicine, Harvard Medical School; Medical Director, George F. Baker Clinic for Chronic Disease at the New England Deaconess Hospital; Consulting Physician, Boston City Hospital, Boston, Mass.

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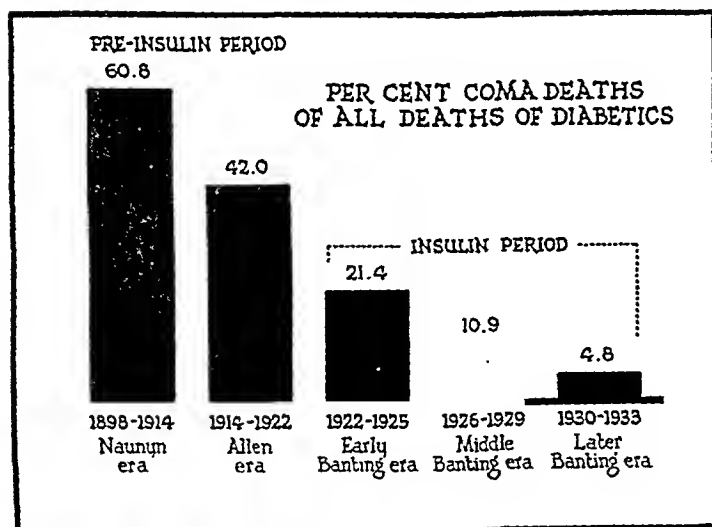


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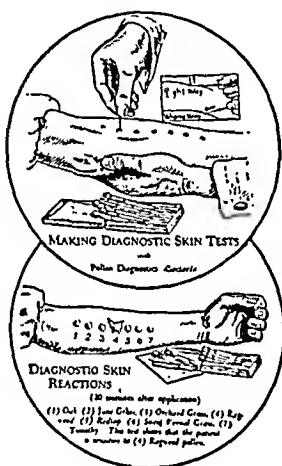
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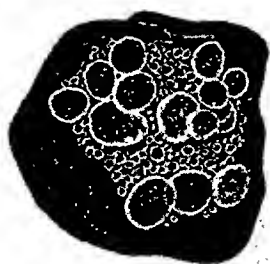
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ORIGINAL ARTICLES.

STUDIES IN DIABETES MELLITUS.

II. ITS INCIDENCE AND THE FACTORS UNDERLYING ITS  
VARIATIONS.

By ELLIOTT P. JOSLIN, M.D.,

CLINICAL PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL; MEDICAL DIRECTOR OF  
THE GEORGE F. BAKER CLINIC, NEW ENGLAND DEACONESS HOSPITAL,  
BOSTON, MASS.

LOUIS I. DUBLIN, PH.D.,

THIRD VICE PRESIDENT AND STATISTICIAN, METROPOLITAN LIFE INSURANCE COMPANY,

AND

HERBERT H. MARKS,

NEW YORK.

(From The George F. Baker Clinic, New England Deaconess Hospital and the Statistical Bureau, Metropolitan Life Insurance Company.)

OUR earlier paper dealt with the characteristics and trends of diabetes mortality. Of equal interest and value are the facts on the morbidity or incidence of the disease in various parts of the world, and in various geographical, social and economic groups. These we shall now consider. We may, then, be in a position to discuss the underlying reasons for these differences.

*Incidence of Diabetes in the United States.* To assess the size of the diabetes problem, it is necessary to know the number of persons who suffer from it. This would be a simple matter if its reporting were compulsory as is the case with certain of the communicable diseases. But since this is not done and is indeed not practicable, we are compelled to resort to other methods. Various estimates



of the number of diabetics have been made for many countries and they differ widely. In the United States, the highest estimate (1% of the population) is unquestionably excessive. It will be worthwhile to examine the available facts which throw light on this important question to see if some reasonable estimate can be made.

First, an approximation of the number of cases may be made from the number of deaths and the average duration of the disease. At the present time, the annual recorded death toll from diabetes in the United States is about 27,000. The true number is considerably higher. Some deaths from diabetes are missed because of faulty diagnosis. In other cases, where the diabetes is under control, the physician may report that the patient died of heart disease, chronic nephritis, cancer or some other diseases of later life, which often complicate diabetes and the death is charged to one of these other causes. The actual number of deaths of diabetics annually may, therefore, run as high as 30,000. The second item of the computation, the duration of the disease, is also uncertain. In Joslin's experience the average duration in fatal cases in the period 1922 to 1926 was 7.6 years, but from 1926 to 1930, 8.4 years. The average duration of these fatal cases is still on the increase and the true figure is now higher than Joslin's latest average. Certainly there has been going on a marked improvement in the duration of life among all classes of diabetics, especially children, since the use of insulin has become general. The average duration of fatal cases today, therefore, is probably more than the previous expectation of life of diabetics. In view of all of the circumstances, we believe that an average of 10 years' duration between onset and death is a conservative estimate. The number of cases today on this basis would approximate the number of deaths per year times the average duration, or 27,000 to 30,000  $\times$  10, or between 270,000 and 300,000 cases.

The several sickness surveys, made from time to time, in various areas are also of value in estimating the incidence of diabetes. The survey of chronic disease in Massachusetts in recent years under the direction of Bigelow and Lombard<sup>1</sup> of the State Department of Health gives us the fullest information on this subject. For this survey, house to house visits were made in various areas of the State and a mixed rural and urban population of approximately 100,000 persons was covered. Special attention was paid to persons over 40 because the investigators were primarily interested in chronic disease. On the basis of this investigation, it was estimated that there were 15,000 diabetics in Massachusetts, or nearly 4 cases of the disease per 1000 inhabitants.

Details regarding age and sex incidence of the Massachusetts survey were available to us through the courtesy of Dr. Lombard. At ages 40 and over, there were twice as many female diabetics as there were males. In both sexes, more than half the cases were

between 50 and 69 years of age, but the age incidence of the disease, relative to the number of persons living, was highest between ages 70 and 79. In that age period, the ratio of diabetic to the total population surveyed was 10.4 for males and 19 per 1,000\* for females. These ratios show a steady rise with age. Between 40 and 49 only 4.2 men and 5 women per M were diabetic. Under age 40 the number of diabetics counted in this survey was too small to be representative; at ages under 20, there were only 6 cases (0.4 per M), and between ages 20 and 39, 20 cases (1.5 per M).

The number of diabetics in the United States would be 500,000, if the incidence of 4 per M registered in Massachusetts prevailed throughout the country. But the population of Massachusetts is older on the average than is the country as a whole. Fortunately, we can bring our estimate a little closer by using the incidence rates, specific for sex and age. This gives between 350,000 and 400,000 diabetics as the probable number. This figure is derived in the following manner: For ages over 40, the incidence in Massachusetts at the various ages for each sex separately has been multiplied by the corresponding populations for the country. Thus, we obtain a total of approximately 325,000 diabetics at ages 40 and over, of whom  $\frac{2}{3}$  are men and  $\frac{1}{3}$ , women (see Table 1). For ages under 40, there would be about 75,000 cases on the basis of the Massachusetts figures, but the basis of the computation cannot be considered very reliable. Some clue to the number of cases at these ages is furnished, however, by the mortality figures in the years preceding insulin treatment. At that time, few young diabetics survived more than a year, particularly at ages under 20. The number of new cases each year is, therefore, approximately equal to the annual toll of deaths from diabetes at that time. Between 1919 and 1921 the average number was 1,400 at ages under 20 and nearly 2,000 between ages 20 and 39. Making allowance for the mortality under present conditions of young diabetics acquiring the disease since 1921, and for the fact that with the lapse of time some of those surviving have graduated into the succeeding age groups, the number of diabetics under 20 may be taken as between 4 and 6 times the annual pre-insulin toll of 1,400, at these ages or between 5,600 and 8,400; and at ages 20 to 39, between 8 and 10 times the 2,000 deaths occurring annually prior to 1922, or between 16,000 and 20,000. The total under 40 by this estimate would be roughly between 22,000 and 30,000.

While the Massachusetts survey is the most comprehensive and most detailed, it will be worthwhile to review other surveys which throw light on this problem of diabetes incidence. Two such studies<sup>2,3</sup> in New York State in 1927 are informative. In Essex County, which is largely rural in nature, investigation disclosed 154

\* Throughout this and other papers of the series "per M" is used to indicate "per thousand persons."

cases of diabetes in a population of approximately 18,000, or nearly 9 cases per M. This county, however, contains an exceptionally large proportion of old persons and we know that the existence of the disease rises rapidly with age. The incidence figure for this county, therefore, is probably higher than average. The second survey in New York State covering a larger area also rural in character, revealed a total of 505 diabetics in an estimated population of 101,000, or an incidence of 5 diabetics per M. This population, too, contained an unduly large proportion of older persons and is also probably higher than the average for the country. The survey of chronic illness in New York City<sup>4</sup> in 1928 covering 20,754 persons chronically ill disclosed 378 (18.2 per M) with diabetes. Of this number, 326 were suffering primarily from diabetes, but in 52 others the diabetes complicated some more serious condition. This high proportion is, one must remember, the incidence of diabetes among persons incapacitated by illness, and not in a general population. Surveys of small populations in Massachusetts<sup>5,6</sup> in 1927 disclosed between 1 and 2 diabetics per M. In the well-known Hagerstown sickness study<sup>7</sup> covering 8,600 persons, 16 cases of diabetes were found (nearly 2 per M).

TABLE 1.—ESTIMATED INCIDENCE OF DIABETES IN THE UNITED STATES, 1930. AGES 40 AND OVER. BY SEX.

Sex, age group.	Massachusetts survey.			United States.	
	Population covered.	Incidence of diabetes.		Population 1930 Census.	Estimated number of diabetics on basis of Massachusetts incidence.
		Number of cases.	Cases per 1,000 population.		
Persons					
Ages 40 and over	45,487	445	....	36,038,981	325,711
Males:					
40 and over . . . .	21,220	146	....	18,632,739	123,765
40 to 49 . . . .	8,048	34	4.2	7,808,383	32,795
50 to 59 . . . .	6,369	42	6.6	5,557,637	36,680
60 to 69 . . . .	4,262	44	10.3	3,359,320	34,601
70 to 79 . . . .	2,018	21	10.4	1,539,251	16,008
80 and over . . . .	499	5	10.0	368,148	3,681
Unknown . . . .	24	....	....	.....	....
Females:					
40 and over . . . .	24,267	299	....	17,406,242	201,946
40 to 49 . . . .	8,556	43	5.0	7,224,091	36,120
50 to 59 . . . .	7,095	107	15.1	5,063,844	76,464
60 to 69 . . . .	5,011	86	17.2	3,162,506	54,395
70 to 79 . . . .	2,637	50	19.0	1,517,143	28,826
80 and over . . . .	928	13	14.0	438,658	6,141
Unknown . . . .	40	....	....	.....	....

The notable study of defects found in men examined for military service<sup>8</sup> during the World War disclosed 740 cases of diabetes (0.27 per M examined). But this low rate is not surprising because most of the 2.5 million men examined were between the ages of 18 and 30 years. The sickness census taken in the course of the famous Framingham demonstration<sup>9</sup> in 1917 showed only 7 diabetics among 6,582 persons. But later in the same year, over 4,000 persons were given a health examination and 11 cases of diabetes were found (over 2 per M).<sup>10</sup> A study of illness in Dutchess County, New York,<sup>11</sup> in 1912 covering 12,000 persons revealed only 7 cases of diabetes

(less than 1 per M). Despite the small number surveyed, it is significant that all 7 cases were residents of towns in the county.

Periodic health examinations also throw some light on the incidence of diabetes. Unfortunately, facts from this source are limited to the incidence of glycosuria. A survey of nearly 17,000 life insurance policyholders examined by the Life Extension Institute in 1921,<sup>12</sup> showed an incidence of 5 cases per M with marked glycosuria (1% or more). In a later study of over 100,000 men,<sup>13</sup> the incidence was found to be 4 in every 1,000. A similar study of nearly 12,000 women<sup>14</sup> also disclosed 4 cases of marked glycosuria per M examined. In interpreting these results, the reader is cautioned that the data is limited almost entirely to adults among whom the incidence of diabetes is much higher than the population at large; that for the most part, only a single urine examination is made and that the glycosuria of 1% or more does not necessarily mean the existence of diabetes. The figures from this source, therefore, are suggestive rather than conclusive.

In view of the great variation in the incidence of recognized cases of diabetes in these several surveys, most of them limited to the East, it seems almost presumptuous to make any definite estimate of the number of cases in this country. It is our judgment, however, that a conservative estimate of the number of known cases is probably at least 2 per M, but more probably between 2.5 and 3 per M. This would place the number of known diabetics between 245,000 and 370,000, or to use round numbers, we may say that 250,000 is a conservative estimate of the number of diabetics in this country and 400,000, a generous and outside estimate. To put it in another way, 1 in every 350 to 500 persons in this country is a diabetic. This estimate excludes, of course, cases of the disease as yet undiagnosed. It is not possible to determine the number of the latter with any degree of accuracy. But there are indications that their number is fairly large. A recent survey of nearly 60,000 applications for life insurance<sup>15</sup> showed that 2.6 per M were rejected because sugar was present in the urine in such amounts and so persistently that it was unsafe to insure these applicants even at a substantial advance in the premiums charged. It is fairly certain that in only a few cases was the applicant aware of his condition before making his application for insurance. Another indication is the fact that in old age diabetes is often very mild and may be present a long time before symptoms of it develop. It is not improbable that undiagnosed cases are about half as numerous as the recognized cases.

The wide range of the incidence of diabetes in the various studies is significant from another point of view. It shows clearly the rapid increase in the frequency of the disease. For example, we may compare the recorded incidence in Dutchess County in 1912—less than 1 per M—and in Framingham in 1917—1.1 per M—with the figure of 4 per M in the recent state wide survey of Massachusetts described above, and the figures of 5 and 9 per M in the rural parts of New

York State. The increase in the frequency of diabetes is also indicated by data of general hospitals. The record of Bellevue and Allied Hospitals in New York is typical. In the 3-year period 1920-1922, 629 patients were treated for diabetes, but in 1928-1930, a period of the same length, the number of such cases was 1,293, or more than double the earlier figure. In the same period, the total number of patients discharged had risen from 171,267 to 217,626, an increase of only 27.1%. The ratio of diabetics to total patients rose in this interval from 3.7 to 5.9 per M.

*Incidence of Diabetes in Other Countries.* In Germany likewise, great interest has been shown in the incidence of diabetes and, fortunately, the data for that country are exceptionally good. A survey by Gottschalk<sup>16</sup> of the whole population of Stettin, a city of 268,000 inhabitants, disclosed 640 diabetics (2.37 per M)—a figure very close to the one we think most reliable for the United States. On the basis of this study, the number of diabetics has been estimated to be 150,000. Grote, however, states that the actual number may be as much as 25% higher because the working capacity of older patients is affected so little that they often do not come to the attention of physicians. The number of diabetics in Germany was estimated to be approximately 120,000 in an earlier statement by Grote. Umber placed the figure between 100,000 and 120,000, based upon his studies of the incidence of diabetes in 1916 in Berlin and its environs.

A much older study, based on the records of the Ortskrankenkasse of Leipzig<sup>17</sup> in 1910, a sickness insurance society with a membership of 1,000,000 men and 250,000 women, showed only 0.2 cases of diabetes per M men and 0.1 per M women. This society included no children as members, however, and was deficient in the proportion of old persons. It was made up, for the most part, of wage earners in the population. On the whole, therefore, the figures understated the incidence of the disease for a population of normal age constitution. Despite this limitation, the great disparity between the early and recent figures clearly brings out the greater frequency of cases of the disease in Germany today. The data on admissions to German general hospitals confirm this trend. Whereas in the years 1877-1879, diabetic patients constituted about 1 in every 2,500 admissions to these hospitals, the proportion increased to 1 in every 400, 30 years later. It has continued to advance so that now 1 in every 200 patients admitted is a diabetic.

The number of diabetics in England and Wales in 1923-1924 was estimated by Young and Russell<sup>18</sup> as about 24,000, and in all of the United Kingdom as 29,000. They based their computation upon the case mortality data of the Leipzig study, cited above. In comparison with the estimated numbers for the United States and Germany, their figures seem too low. If the average lifetime subsequent to onset of diabetes is taken at 10 years, as in one of our estimates for the United States, the annual toll of diabetes deaths, which is now

close to 6,000 in England and Wales, indicates an incidence of nearly 60,000, at present. For the United Kingdom the number would be approximately 70,000.

In Denmark, Norgaard<sup>19</sup> estimated the number of diabetics in 1932 to be between 5,000 and 6,000 (an incidence of 1.5 per M). The diabetic population of the country has been increasing very rapidly. In 1927 it was estimated that there were little more than 4,000 cases of the disease. Hospital data for Copenhagen also illustrate the problem admirably. In 1890 only 10 diabetics were treated in the hospitals of that city. In 1924 this figure had mounted to 608.

The number of diabetics in Sweden was estimated by Lundberg<sup>20</sup> at 1% of the population, or 61,000. But the figure is too high. For Switzerland the incidence in Basle was estimated by Hunziker<sup>21</sup> in 1918-1919, at 1.54 per M on the basis of information from food-cards required in war time. The frequency of the disease is probably greater today. Rabinowitch<sup>22</sup> estimates the incidence in Canada at 1% of the population, or over 100,000. This is unquestionably too high because the death rate from the disease in that country is much lower than in the United States, and its population is younger than ours. According to the latest censuses, the median age in Canada (1931) is 24.8 and in our white population (1930) is 26.9 years. It is probable that the number of known cases in Canada does not exceed 30,000. The incidence in France and other countries is unknown, as the basic data for estimating it are not available.

*The Chances of Dying from Diabetes.* We have already shown that the number of known diabetics in this country is probably under 400,000. This number does not, however, give us a true picture of the real importance of diabetes. Analysis of mortality data shows that over 2.5 million persons, or 2.08% of the population living in 1930 may be expected to succumb eventually to diabetes, if current death rates from the disease continue to prevail during the next generation. In our white population, diabetes may be expected to account for 2.19% of the deaths of those living in 1930; in our colored population, for 1.11%. For females, ratios are far higher than for males, thus 2.78% of the deaths of white females in the 1930 population may be expected to occur from diabetes, but only 1.61% of the deaths of males. For colored females, the expected ratio is 1.49%, but only 0.74% for colored males.

These results are obtained by computing for each age group of the population the number of persons who may be expected ultimately to die of diabetes. This can be done by the aid of a life table and of the actual proportions out of the total deaths at each age that occurred from diabetes. On the basis of these data, we can compute the proportion of all persons now of a given age—for example, 10 years—who will ultimately die of diabetes, or as we may say, the probability at age 10 of ultimately dying of diabetes.

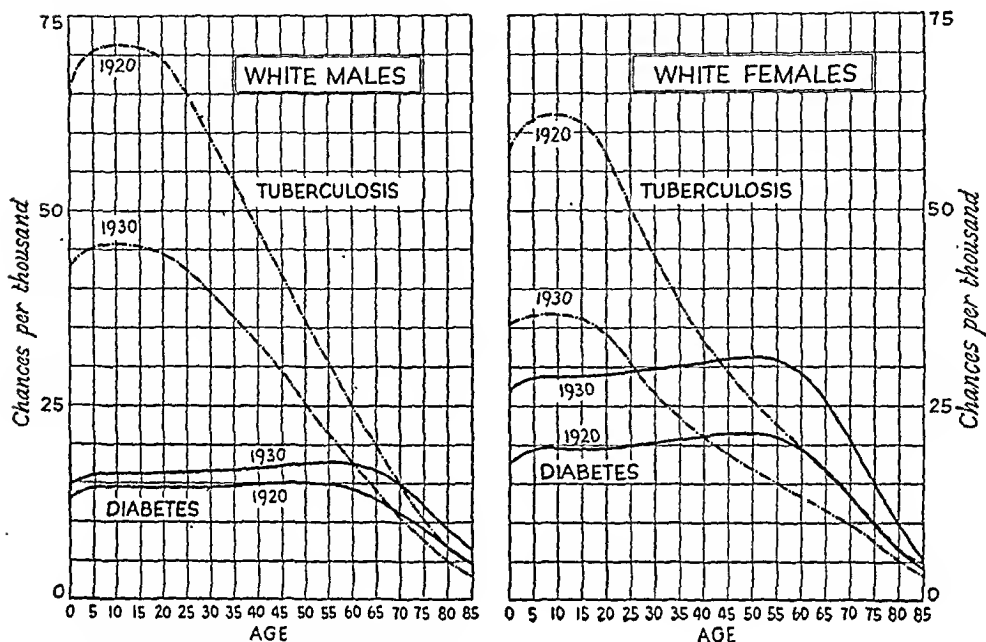
We have computed the chances of eventually dying from the disease at successive ages of life for the two sexes separately, according to the mortality statistics of 1920 and 1930. Nothing illustrates the seriousness of the diabetes problem better than these figures. Thus, 15 white males per M born will eventually die from diabetes if the 1930 death rates continue, and 27 females per M born. Only 10 years earlier these probabilities at birth were only 13 per M for white males and 18 for white females. Thus, this probability has increased nearly  $\frac{1}{6}$  for males and  $\frac{1}{2}$  for females within a decade. Because of the greater increase in female mortality from diabetes, the excess of the female rate over the male reached 81% in 1930, compared with but 37% a decade earlier.

The chances of dying from diabetes vary with age. Among males there is a definite increase in the probability between birth and age 5 and a very gradual increase thereafter until well past middle life. On the basis of 1930 death rates, the maximum probability for males was reached at about age 55 when nearly 18 in each M living would be expected to die eventually from diabetes. At every age these probabilities are much higher for males on the basis of 1930 rates than in 1920.

Among females, too, there is a marked increase between birth and age 5 in the probability of dying from diabetes, and a gradual increase thereafter until past middle life. The maximum probability is, however, reached about 5 years earlier in the case of females, that is, about age 50. At that age, on the basis of 1930 death rates, 31 women per M may be expected eventually to succumb to the disease. After age 50 the probability declines at first slowly, but then sharply so that at age 80 this probability of dying from the disease is only 10 per M. Again, as in the case of males, the probabilities at every age, based on 1930 death rates, are much higher than on the basis of death rates of but a decade earlier. The excess is consistently about 50%.

It will be appreciated how far diabetes has advanced to its present importance as a factor in mortality by comparing the probabilities of ultimately dying from it with the probabilities of dying from tuberculosis (Chart I). On the basis of conditions in 1930, for women past 30, the probability of dying from diabetes is greater than from tuberculosis. In 1920 this did not occur until age 65 was reached. Among men the situation is different. The probability of dying from diabetes does not exceed that of tuberculosis until age 65, but in 1920 this did not occur until age 80. Moreover, under 1920 conditions the margin at the older ages between these probabilities for diabetes and tuberculosis was small, whereas under the mortality conditions prevailing in 1930 the probability of dying from diabetes is 50% higher than that for tuberculosis for women at 40, and more than twice as great at ages past 60. Among men, too, similar differences exist, though not at all so marked.

Let us now look into the incidence of diabetes in various geographical, racial and social groups. Here we are limited to mortality data to guide us, for either there are no data on morbidity for most of these items, or such facts as do exist are too fragmentary or specialized to be very reliable.



\* Data relate to Death Registration States as of 1920

CHART I.—Chances of eventually dying from diabetes and from tuberculosis. United States\* 1920 and 1930.

*Urban and Rural Mortality from Diabetes.* Diabetes mortality in the cities and towns is usually much higher than in the countryside. In this country† in 1929 the death rate in the urban part of the Registration States was 24.2 per 100,000, but only 14.2 in the rural areas, and for the 5 years ending in 1929, 23 and 13.8 respec-

\* Data relate to Death Registration States as of 1920.

† Certain limitations of this material should be noted. (1) Available mortality data on the urban and rural populations are based upon crude death rates and thus do not take into account the differences in the sex and age composition of these populations. Correction for the factor of age would tend to increase somewhat the disparity between the urban and rural population of the country as a whole, but correction for the factor of sex would decrease it. In some parts of the country, however, the proportion of old persons is greater in the urban population; in others, it is greater in the rural population. (2) The practice of registration offices to charge deaths according to the place of occurrence also affects the death rates. Many deaths of farm dwellers from diabetes occur in cities where these people go for treatment. Investigation shows, however, that even when this has been allowed for, there is a substantial excess for the urban areas.<sup>21</sup> (3) Urban death rates relate to the population in communities of 10,000 or over. Towns of smaller size are classed as rural for purposes of mortality statistics and such communities contain a sizeable proportion of the "rural" population of the country—nearly 17% in 1930.



tively. Thus, for the country as a whole, the excess of the urban rate in recent years has been approximately 70%. This situation is a very general one. As Table 2 shows, in only 4 states did the death rate in the rural areas exceed that in the cities during the 2-year period 1928-1929. In these cases, an exceptionally high proportion of old persons in the rural population, or of young persons in the

TABLE 2.—DIABETES MORTALITY IN URBAN AND RURAL AREAS IN THE U. S.

Mean Death Rate Per 100,000, 1928-1929. White Persons. By State.

State.	Total.	Urban.	Rural.
<i>Registration States</i> . . . .	19.0	24.4	14.3
Rhode Island . . . .	26.9	26.9	27.4
New York . . . .	26.7	28.2	21.3
New Hampshire . . . .	26.0	25.6	26.4
Vermont . . . .	25.5	41.9	22.6
Maine . . . .	25.1	31.5	22.6
Illinois . . . .	23.6	26.2	19.6
New Jersey . . . .	23.3	27.3	17.7
Connecticut . . . .	23.0	24.8	17.8
Massachusetts . . . .	22.7	23.3	19.7
Pennsylvania . . . .	22.6	26.8	18.6
Maryland . . . .	22.5	27.1	16.7
Nebraska . . . .	22.3	30.7	19.7
Delaware . . . .	21.4	25.8	17.4
Indiana . . . .	21.3	23.2	19.9
Ohio . . . .	21.3	22.8	19.5
Wisconsin . . . .	20.8	25.4	17.6
Kansas . . . .	20.6	25.8	18.8
Missouri . . . .	20.6	27.0	16.3
Minnesota . . . .	20.1	22.1	19.0
Michigan . . . .	19.3	19.1	19.5
Iowa . . . .	19.1	24.5	17.0
California . . . .	19.0	21.5	15.6
Washington . . . .	18.2	23.0	14.0
Oregon . . . .	17.5	22.4	14.6
Montana . . . .	16.6	28.1	13.1
Utah . . . .	15.9	23.1	11.5
Colorado . . . .	15.5	20.0	12.6
North Dakota . . . .	15.4	29.4	14.0
Florida . . . .	14.5	19.2	12.3
Nevada* . . . .	14.4	17.1	13.7
Louisiana . . . .	13.2	24.2	7.8
Kentucky . . . .	12.6	27.5	9.0
Virginia . . . .	12.6	17.6	11.0
Idaho . . . .	12.3	27.0	10.9
Wyoming . . . .	12.2	11.1	12.4
Georgia . . . .	11.5	19.1	9.4
South Carolina . . . .	11.1	25.4	8.9
Mississippi . . . .	10.7	21.2	9.4
West Virginia . . . .	10.3	18.1	8.4
Tennessee . . . .	10.1	19.1	7.9
Alabama . . . .	9.9	18.8	7.9
New Mexico* . . . .	9.6	23.4	8.6
North Carolina . . . .	9.5	18.3	8.0
Oklahoma . . . .	9.2	14.5	7.9
Arizona . . . .	8.8	17.0	6.8
Arkansas . . . .	8.3	17.7	7.4

\* Death rate in 1929, year of admission to Registration Area.

urban population, is a prime reason for the excess of the rural rates. Fluctuations due to chance may also be involved, in the case of Rhode Island, because of its very small rural population; and in Wyoming, because of its very small urban population. The higher incidence of diabetes in urban areas indicated by the mortality figures is confirmed by the Massachusetts survey of chronic illness.

In England and Wales, on the other hand, crude death rates from diabetes in the cities have been lower than in the countryside. Indeed, 1930 was the only year in the past decade when the urban death rate was higher. When, however, the death rates for both populations are adjusted for differences in age and sex composition, the rural death rate has been found consistently lower, but the difference is much smaller than in this country. In Denmark, as in the United States, the urban death rates from diabetes are much higher than in the country and have been ever since figures began to be compiled over a decade ago. In 1931 the urban death rate in that country was 18.6 per 100,000, but only 13.9 in the rural areas. The urban death rate was thus about 35% higher than the rural rate.

TABLE 3.—TRENDS IN URBAN AND RURAL MORTALITY FROM DIABETES. U. S.  
REGISTRATION STATES, NEW YORK, MICHIGAN AND WISCONSIN, 1900-1929.

Year.	U. S. Registration States.		Death Rate Per 100,000.							
	Urban.	Rural.	New York.		Michigan.		Wisconsin.			
			Urban.	Rural.	Urban.	Rural.	Urban.	Rural.		
1929	24.2	14.2	27.6	23.8	18.7	20.0	24.6	15.5		
1928	24.6	14.4	28.2	18.5	19.1	18.9	25.9	19.7		
1927	22.4	13.3	25.0	21.5	18.0	17.2	24.2	17.0		
1926	22.6	13.9	26.0	20.3	17.6	16.4	19.6	15.7		
1925	21.1	13.1	24.3	19.8	18.0	16.5	20.1	18.0		
1924	20.2	13.4	24.0	19.0	14.4	17.8	19.1	13.8		
1923	21.9	14.3	26.2	20.9	16.9	18.2	22.8	18.2		
1922	22.4	14.9	27.1	23.8	17.0	18.2	22.8	18.3		
1921	20.2	13.6	23.8	20.8	13.5	19.5	18.1	17.1		
1920	19.4	13.1	23.8	21.4	15.0	17.5	21.8	16.9		
1919	18.0	12.2	21.4	20.6	17.7	18.1	17.0	14.4		
1918	18.8	13.4	22.5	22.1	18.3	19.2	16.5	15.2		
1917	20.3	14.1	23.3	23.4	19.5	19.0	16.7	16.3		
1916	20.0	14.4	22.1	20.4	18.1	17.1	19.3	16.5		
1915	20.1	15.4	23.6	24.6	19.3	17.4	19.1	18.0		
1914	18.4	14.3	20.8	21.2	15.6	17.7	17.5	14.6		
1913	17.5	13.4	19.1	18.3	15.8	16.7	17.3	14.5		
1912	16.9	13.1	18.3	16.8	16.1	14.2	16.3	13.6		
1911	17.0	13.0	18.9	19.5	13.5	15.0	16.5	13.5		
1910	16.8	13.5	18.3	18.9	14.6	14.9	14.5	12.6		
1909	15.3	12.8								
1908	14.5	12.9								
1907	15.4	12.8								
1906	14.5	12.0								
1905	14.8	13.3								
1904	14.9	13.3								
1903	13.0	12.1								
1902	11.8	11.5								
1901	12.1	10.8								
1900	11.1	10.8								

*Trends of Diabetes in Urban and Rural Areas.* The trend of diabetes mortality in the cities of this country has been sharply upward; in the rural part it has been much steadier. The figures for these areas (Table 3), do not, however, give a true picture of the situation, particularly in the rural population, because the states admitted to the Registration Area more recently have had lower diabetes rates than prevailed in the original states. The true situation is portrayed more accurately by the figures for diabetes mortality in New York, Michigan and Wisconsin, 3 states with large urban and rural populations. These figures, also given in Table 3, show appreciable increases in the rural death rates from diabetes since 1910, though not as great as in urban areas. Thus, in New York the rural death rate from diabetes in 1925-1929 was 10.1% higher than in 1910-1914, but the urban rate was 37.2% higher; in Wisconsin, the rise was 24.6 in the rural diabetes rate but 39.6% in the urban areas. In Michigan, the increase in the rural rates has been 13.4%, while that in the urban was 21.2%.

In England and Wales in the last decade, the trend of the diabetes rates in both urban and rural areas has been upward, especially in the former. Thus, the urban rate in 1931 was 30% higher than the rate in 1921-1922, but the rural death rate in the same period had increased by only 23%. In Denmark, too, diabetes death rates have been increasing in recent years both in the urban and rural populations. Between 1922 and 1926 following the introduction of insulin, the diabetes death rate in the cities fell sharply, but since 1926, the rate has shown a sharp and continuous advance. The 1931 death rate was the highest on record. The death rate in rural Denmark in 1931 was also higher than any previously recorded with a fairly steady rise since 1924. In comparison with the 1920 rates, there has been an increase of about 30% in the case of the cities, and of 25% in the rural areas. The figures for England and Denmark are given in Table 4.

TABLE 4.—TRENDS IN URBAN AND RURAL MORTALITY FROM DIABETES. ENGLAND AND WALES AND DENMARK, 1920-1931.

Year.	Death rate per 100,000 England and Wales.		Death rate per 100,000 Denmark.	
	Urban.	Rural.	Urban.	Rural.
1931 . .	14.4	15.2	18.6	13.9
1930 . .	14.3	14.2	16.8	12.7
1929 . .	14.1	14.8	15.8	11.2
1928 . .	12.9	14.4	15.5	11.7
1927 . .	12.6	12.9	15.4	11.2
1926 . .	11.3	12.8	14.3	12.1
1925 . .	11.0	12.1	16.2	10.8
1924 . .	10.8	12.0	16.2	9.8
1923 . .	11.3	12.0	16.6	12.5
1922 . .	11.7	12.8	20.2	11.2
1921 . .	10.5	12.0	17.8	11.9
1920 . .	9.9	10.4	14.5	11.0

**Regional Differences.** *United States.* In the years 1928-1929, the highest diabetes death rate in this country was registered in Rhode Island, 26.9, per 100,000 closely followed by New York with a rate of 26.7. Going back to Table 2, we find that the rates in the New England and Middle Atlantic States were high, all 9 of them being included among the 10 states with the highest rates. The states at the lower end of the scale are, for the most part, the Southern States, or the more sparsely settled states. The rates in the north-eastern states are 2 to 3 times those of the Southern States. The rates used relate to white persons only. The low mortality recorded in the Southern States is, therefore, not due to the lower mortality of the large negro population. In the important agricultural states of the Middle West, the rates tend to approximate the average for the country.

These regional differences in diabetes rates in part reflect merely differences in the composition of the population. High rates prevail in states with relatively large urban populations, and low rates in those with large rural populations. This fact alone explains part of these regional differences. It is interesting and perhaps significant that there is less variability in the diabetes rates of the urban portions of the various states than in the rural rates. Thus the highest urban rates are found in Vermont (41.9), Maine (31.5) and Nebraska (30.7). In few states are the urban rates much below 20. In the rural population, on the other hand, the rates vary from less than 8 in 6 states to 20 or over in 5 states. The rates in rural regions tend to be especially low in the south. There is, it is true, some association between the level of the urban and rural rates in the individual states, but the relationship is not at all consistent. The reader is again cautioned that these rates are not adjusted to eliminate age and sex differentials in these various states and consequently the possibility of differences from these sources must be kept in mind.

*Europe.* Diabetes mortality tends to be high in the countries of northern and western Europe and low in the southern countries. In the Netherlands, the rate—17.7 in 1931—is the highest on that continent. Belgium and Denmark suffered the next highest rates, 15.9 per 100,000 in both cases. The lowest rates for European countries for which we have mortality records, are found in Spain, Italy and Czechoslovakia and are only about half that of the Netherlands. The rates for European countries may be found in Table 2 of our first paper.<sup>24</sup>

Presumably the incidence of diabetes varies in much the same way, but of this we cannot be certain. Unfortunately only for the countries of Northern Europe do we have any estimates of incidence, and even these are only approximations. Again, we are dealing with crude mortality rates and data to adjust them for sex and age differences in the populations of these countries are not generally available. In part, at least, the differences are explicable on the

basis of these factors alone. For, recent figures on age distribution of a few countries indicate that the level of the diabetes mortality rate in these countries tends to reflect the proportion of old persons. To some extent, also, the differences in the rates reflect variations in methods of classifying causes of death. This factor is not a measurable one, but fortunately in most countries of Northern Europe at least, death registration is of a high order and such differences\* as exist affect the rates from diabetes less than most causes of death.

**Racial and National Differences.** *General.* There is in a broad sense, some correspondence between regional, national and racial areas. The regional data just presented should, therefore, indicate that higher diabetes death rates prevail among Teutonic peoples than among Latins and Slavs. Our data on the last named are, however, most deficient. One cannot do more than make this broad generalization because pure racial lines are the exception rather than the rule; so great has been the admixture of the various European Stocks. The diabetes mortality of the colored races, as our first paper has shown, is lower than for the white. Mills,<sup>25</sup> who resided in China for 2 years, observed that among the Chinese diabetes was relatively infrequent and mild in character. He also quotes others on the rarity and mildness of the disease in Japan, the Philippines, India, the Sudan, West Africa and in Venezuela. In the East, it is reported with frequency only among the wealthy and leisured classes; and the adoption of western diets is given as a possible reason for it.

*United States.* Differences in diabetes mortality exist among the many racial stocks in this country. The facts are not clear-cut, however, because the data are based upon national origin, which is often not at all synonymous with racial origin. The material is also rather limited. The only facts of value are on mortality according to country of birth of mother for 1920 and of the foreign born in 1910. Only in New York State and in Pennsylvania were there sufficient persons in the several nationality groups upon which comparisons could be made. Further difficulty arose from the rearrangement of national boundaries as a result of the World War. Despite these difficulties, however, we find a surprising degree of agreement in the studies so far made. In general, diabetes death rates of those of native birth in these two large states were found to be average or even lower. In New York State, persons of Russian origin or Austro-Hungarian origin (most of whom were Jews) had high death rates from diabetes. In Pennsylvania, on the other hand,

\* They are of two origins: (1) Varying procedure in the assignment of the determining cause of death where two or more are stated; (2) the proportion of deaths in which the certifying physician has reported only the terminal conditions, or stated the cause in indefinite, or unsatisfactory terms (senility, "sudden" death, hypostatic pneumonia, dropsy, etc.). Some registration offices try to ascertain the true cause of death in such cases.

the diabetes rates among persons of these origins were lower than in New York State, especially as regards Austria-Hungary. These differences were probably due to the smaller proportion of Jews among persons of these national origins in that state than in New York. Persons of German origin and of Irish origin also had average or above average rates. In contrast, the mortality for persons of Italian parentage was extremely low in both states.

A surprising feature of these experiences is the high mortality found among the Irish. It has been generally assumed that the diabetes rate in this group is low. The basis for this assumption is probably the low diabetes rate prevailing in Ireland and the high mortality which the Irish suffer from tuberculosis. That high tuberculosis rates are associated with low diabetes rates and *vice versa* is an impression very general but not altogether well founded. The reason for the high diabetes mortality of the Irish here is not far to seek. The level of well-being and prosperity among the Irish in this country is far higher than in Ireland itself. Another item—not a negligible one—is that at the time covered in these studies, a disproportionate number of the Irish engaged in the liquor business, an occupation in which, as we shall see later, diabetes mortality is exceptionally heavy.

Table 5 gives detailed figures for Pennsylvania and New York in 1910. These relate solely to the native born and the foreign born. Because of the age of the material, the authors present it with some hesitation, but unfortunately no better data exist. Data for 1920 are not reproduced here because the Census Bureau did not consider the facts on persons of Russian and Austrian maternal parentage sufficiently reliable.

TABLE 5.—DIABETES AND NATIONALITY.

Standardized Death Rates per 100,000 White Persons in New York State and Pennsylvania by Country of Birth, 1910. By Sex for Specified Ages.

Sex, age groups.	United States.		Austria-Hungary.		England, Scotland, and Wales.		Germany.		Ireland.		Italy.		Russia.	
	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.
NEW YORK STATE:														
All ages . . . .	15.4	16.1	15.0	32.7	15.1	18.8	22.1	28.9	18.4	28.7	4.1	8.0	18.3	26.4
25 to 64 . . . .	21.1	21.6	16.2	29.7	19.5	29.3	29.8	41.6	30.8	46.2	9.4	14.1	17.8	35.9
PENNSYLVANIA:														
All ages . . . .	11.4	14.5	0.6	7.9*	13.9	19.2	14.3	20.3	14.1	19.6	2.5*	10.4*	9.2*	15.8*
25 to 64 . . . .	14.1	18.7	1.3	17.4*	7.8	33.3	18.6	31.2	24.8	27.2	5.8*	18.1*	5.8*	19.2*

M. = Male. F. = Female.

\* Based on less than 10 deaths from diabetes.

Particular interest attaches to the diabetes mortality of the Jews. Observations made all over the world indicate a greater frequency of diabetes among them, as compared with other peoples. Physicians treating large numbers of diabetics have frequently commented

upon the disproportionate number of Jewish patients. The high incidence of diabetes in Jews is observed in the facts on mortality of foreign race stocks in this country. Supporting data on this subject are abundant but often of uncertain quality. Probably the best material on the subject is contained in the Jewish Communal Survey of Greater New York.<sup>26</sup> This is reproduced in Table 6, which compares the diabetes mortality of the Jewish population in certain areas of the city in 1925, with that of the total population of the city. It is interesting to note that the crude rate of the Jews is little higher than that of the general population because they are a very young group. When the rates are adjusted for age, however, the Jewish rate is 50% higher than the general city rate. The lower rates of the Jews at the younger ages may simply be due to chance because the number of deaths from diabetes in that year was small. It may possibly be due to the better treatment obtained by young Jewish diabetics. Past 45, the rates for Jews are higher and in old age are double the general rate.

TABLE 6.—DIABETES AMONG JEWS. DEATH RATES PER 100,000. JEWISH AND TOTAL POPULATION IN NEW YORK CITY COMPARED, 1925.

Age groups.	Jewish population.	Total population.
All ages, standardized . . . . .	35.8	24.4
crude . . . . .	24.7	22.3
Under 25 . . . . .	0.4*	0.9
25 to 34 . . . . .	2.2*	2.2
35 to 44 . . . . .	7.2	8.1
45 to 54 . . . . .	60.2	39.2
55 to 64 . . . . .	170.4	134.2
65 to 74 . . . . .	360.1	239.4
75 and over . . . . .	506.7	232.1

\* Based on less than 10 deaths.

The high incidence of diabetes among Jews was also shown by Bolduan and Weiner<sup>27</sup> who compared the proportion of deaths from diabetes to the total deaths among Jews and non-Jews in New York City in 1931. Their material consisted of the death certificates of persons buried in strictly sectarian cemeteries. The proportion of diabetes deaths at all ages (Table 7) was nearly 80% higher among Jews than non-Jews. This excess was found to exist both among males and females, but was largely restricted to the more advanced ages. Under 45 there was only a slight excess in the proportion of diabetes deaths among Jews. It is interesting to note that the proportion of such deaths among Jewish women between ages 55 and 64 reached the amazing figure of 11.5%. Somewhat greater differences in diabetes incidence between Jews and non-Jews were found by DePorte<sup>28</sup> in a similar analysis of death records for 1925 in New York State, outside of New York City. Similar results were obtained in earlier studies of mortality for Boston in 1895 to 1913, by Morrison;<sup>29</sup> for Budapest in 1902 to 1907, by Auerbach;<sup>30</sup> for New York City in

1900, by Stern;<sup>31</sup> for Frankfurt-A. M. in 1872 to 1890, by Wallach;<sup>32</sup> and in the United States in 1890, by Billings.<sup>33</sup> It should be pointed out that differences in the total death rates of Jews and non-Jews have a serious effect on the accuracy of comparisons of this type.\* Fortunately, the differences in the proportions of diabetes deaths among Jews and non-Jews are so great that we may safely accept the figures as good evidence of difference though not as accurate measures of their degree.

TABLE 7.—DIABETES AMONG JEWS. PER CENT DIABETES DEATHS OF TOTAL DEATHS AMONG JEWS AND NON-JEWS. BY SEX AND AGE, NEW YORK CITY, 1931.  
Per cent diabetes deaths of total deaths.

Age groups.	Males.		Females.	
	Jewish.	Non-Jewish.	Jewish.	Non-Jewish.
All ages . . . . .	2.5	1.4	6.3	3.6
Under 25 . . . . .	0.2*	0.1*	0.6*	0.2†
25 to 44 . . . . .	0.9*	0.8	1.2	1.1
45 to 54 . . . . .	2.3	1.6	8.1	5.4
55 to 64 . . . . .	4.0	2.0	11.5	6.6
65 to 74 . . . . .	3.7	2.7	8.3	5.5
75 and over . . . . .	2.3	1.5	4.3	2.5

The lower than average diabetes mortality of most of the colored groups in this country was brought out in our first paper. This applies to negroes, Indians and Japanese. The Chinese in this country have a high rate, but this group is made up chiefly of adult men. In China itself, the disease is relatively uncommon, according to Mills<sup>34</sup> observation, cited above. On the other hand, he has also observed from his contact with Chinese students, that on European diets they easily develop boils and a mild glycosuria. These factors and the abnormal living conditions of the Chinese in this country probably indicate the reasons for their high diabetes mortality here.

*Social and Economic Differences in Diabetes Incidence.* Diabetes mortality differs in the various strata of society. The latest study of this subject relates to males in England and Wales in the years 1921 to 1923.<sup>35</sup> The special report of the Registrar-General on mortality according to social classes classified the male population into 5 main groups as follows: Class I, professions and the higher ranks of business life; Class II, farm owners, retail merchants, clerical workers, teachers and the like; Class III, skilled workers, sales clerks, etc.; Class IV, semiskilled workers, including agricultural laborers; and Class V, unskilled workers.

The highest diabetes death rate was recorded in Class II and the next highest, in Class I. With this exception, diabetes mortality is highest in the upper classes and decreases progressively with each successive grade of social standing. Thus, the mortality in Class I was 25% above average for all occupied and retired civilians, and

\* If, for example, at a stated age, the total death rate of one group is 20% lower than that of the other, identical diabetes rates would yield a proportion of diabetes deaths 25% higher in the former than in the latter.

† Based on less than 10 deaths.



in Class II, 45% above, but in Class III nearly 10% below the average, in Class IV, nearly 25% below and in Class V, nearly 35% below. The mortality in Class II is well over twice as high as that in the lowest groups in the social scale. These findings are in general agreement with the earlier English study<sup>36</sup> along these lines (1910-1912).

The differences in the diabetes mortality in the various social classes vary with age. Generally speaking the differences are least in younger persons and most in old age. The mortality in Class II is highest, but past 65, the rank goes to Class I. In old age, the mortality in these two upper social classes is from 4 to 5 times as high as among unskilled workers. Data from the Registrar-General's report are given in Table 8.

TABLE 8.—DIABETES AND SOCIAL.

Death Rates per 100,000 Among Males, Aged 16 and Over, Classified According to Social Status and the Ratio of the Rate in Each Class to that of all Occupied and Retired Civilians by Age. England and Wales, 1921 to 1923.

Age group.	Death rate per 100,000.					Per cent of death rate of all occupied and retired civilians.				
	All occupied and retired civilians.	Social class.					Social class.			
		I.	II.	III.	IV.	V.	I.	II.	III.	IV.
All ages: 20 to 65*	12.2	15.2	17.7	11.2	9.2	8.1	124.6	145.1	91.8	75.4
16 to 19 . . . . .	3.3	2.6	2.3	3.8	3.2	2.8	78.8	69.7	115.2	97.0
20 to 24 . . . . .	4.5	4.3	5.1	4.5	4.3	4.2	95.6	113.3	100.0	95.6
25 to 34 . . . . .	5.5	6.3	7.1	5.3	4.7	5.2	114.5	129.1	96.4	85.5
35 to 44 . . . . .	6.7	4.7	8.0	6.6	6.6	5.2	70.1	119.4	98.5	98.5
45 to 54 . . . . .	12.8	19.0	19.3	11.5	8.9	10.7	148.4	150.8	89.8	69.5
55 to 64 . . . . .	32.4	46.8	55.1	30.4	21.4	14.5	144.4	170.1	93.8	66.0
65 to 69 . . . . .	65.3	153.0	114.3	61.2	36.2	26.5	234.3	175.0	93.7	55.4
70 and over . . . . .	99.7	203.9	177.2	71.7	56.4	45.7	204.5	177.7	71.9	56.6

\* Standardized.

*Diabetes and Occupation.* It is to be regretted that no authentic data are available on the incidence of diabetes in various occupations. The reports of the Registrar-General give the most instructive information but are based on mortality. Table 9 indicates why the mortality in the two upper social classes is higher than in the working classes; for among occupations with high rates are auctioneers, commercial travellers, farm owners, physicians, teachers, office workers and certain types of tradesmen. The persons following these occupations are classified in the two upper social classes.

The most striking feature of the table, however, is that the highest mortality is recorded for persons engaged in occupations relating to the distribution and serving of food and drink. Thus, the mortality of inn- and hotelkeepers and publicans is 285% of the average, the highest recorded for any large occupational group. Not far behind are to be found both sales clerks and owners of businesses for the sale of meat, fish, grocery and provisions. Bakers and pastry

TABLE 9.—DIABETES AND OCCUPATION. STANDARDIZED MORTALITY AMONG MALES AGED 20 TO 65 IN SPECIFIED OCCUPATIONS† COMPARED WITH THAT OF ALL OCCUPIED AND RETIRED CIVILIAN MALES TAKEN AS 100. ENGLAND AND WALES, 1921-1923.

High mortality.		Average mortality.		Low mortality.	
Occupation and social class.	Mortality ratio.	Occupation and social class.	Mortality ratio.	Occupation and social class.	Mortality ratio.
Inn, hotelkeepers, publicans (II)	285	Railway clerks (II)	111	Coal mine—underground workers, not hewers or superintending staff (IV)	85
Woolen and worsted weavers* (III)	257	Civil service officials and clerks (II)	107	Carpenters, coach builders, pattern makers and similar occupations (III)	82
Auctioneers, appraisers, valuers (I)	220	Bakers and pastry cooks (III)	102	Proprietors, etc., of businesses for the sale of textiles and clothing (II)	80
Salesmen, etc., in businesses for sale of fish, meat, green grocery, milk (III)	203	Drivers of horse-drawn vehicles (IV)	101	General and undefined laborers (V)	79
Salesmen, etc., in businesses for the sale of grocery and provisions (III)	190	Tailors; tailors' pressers and machinists ALL OCCUPIED AND RETIRED MALES (= AVERAGE)	100	Coal mine—workers above ground, not superintending staff (IV)	79
Proprietors, etc., of businesses for sale of fish, meat, green grocery, milk (II)	183	Insurance agents and canvassers (III)	99	Clergymen (Anglican Church) (I)	78
Proprietors, etc., of businesses for the sale of grocery and provisions (II)	177	Warehousemen (II)	96	Machine tool workers and metal spinners* (III, IV)	76
Dye mixers and dyers* (IV)	160	Coal mine—persons conveying material to the shaft (IV)	90	Gardeners and their laborers (III, V)	65
Commercial travellers (II)	159	Fitters, toolsetters, millwrights, and similar occupations (III)	89	Coal miners—not superintending staff (III, IV)	64
Registered medical practitioners (I)	156	Painters and decorators (II)	89	Agricultural laborers (including shepherds) (IV)	60
Proprietors and managers of wholesale or retail dealing businesses (II)	148	Drivers of motor vehicles and steam wagons (III)	88	Bricklayers (III)	60
Salesmen and shop assistants (III)	146	Coal mine—other workers below ground (IV)	86	Contractors' laborers; navvies (V)	60
Railway signalmen (III)	142			Other dock laborers* (V)	56
Locomotive engine drivers, firemen, cleaners (II)	134			Coal mine—subordinate superintending staff* (III)	56
Farmers and their relatives (II)	131			Coal mine—hewers and getters (III)	46
Railway officials, station masters, etc. (II)	127			Building-trade laborers (V)	43
Employers, managers in building, etc., trades; clerks of works (II)	121			Farm bailiffs and foremen* (III)	29
Smiths and skilled forge workers (III)	121				
Railway porters and lampmen (IV)	121				
Clerks (not civil service or local authority); typists (II)	118				
Stationary engine and crane drivers (II)	117				
Teachers (not music teachers) (II)	116				
Local authority officials and clerks (II)	116				

\* Occupational groups with 15-24 deaths from diabetes. All other groups had 25 or more deaths.

† Mortalities are classified by size of mortality ratio as follows: High, 115 or more; low, 85 or less; average, 84-114. Figures in parentheses indicate the social class in which the occupational group is classified.

cooks surprisingly have a diabetes mortality only a little higher than average. Other groups with significantly high rates are various types of railway workers.

At the other end of the scale, we find consistently that workers doing hard manual labor experience the minimum rates from diabetes. For example, the mortality of building-trade laborers is only 43% of the average for all occupied persons; of coal-mine hewers and getters, only 46%; of dock laborers, 56%; and of contractors' laborers and navvies, only 60%. One group with a low mortality which does not fit in with this general picture is that of clergymen belonging to the Anglican Church who have a mortality 22% better than the average for all occupied persons.

American data tend to confirm these results. The only available source in this country is the mortality experience of the Industrial Department of the Metropolitan Life Insurance Company.<sup>37</sup> Most of the men in this experience are wage earners and the representation of persons in the highest economic grades is small. Analysis of the deaths during 1922-1924 revealed a high diabetes mortality among merchants and storekeepers, office workers and also among saloonkeepers and certain types of railway workers. Laborers, miners and farm workers had a low mortality. Table 10 gives the figures for the larger occupational groups in this experience.

TABLE 10.—DIABETES AND OCCUPATION. OCCUPATIONS IN ORDER OF RANK OF MORTALITY FROM DIABETES.\* METROPOLITAN LIFE INSURANCE COMPANY, INDUSTRIAL DEPARTMENT, 1922-1924.

Occupation.	Standardized relative index, ages 15 to 64†
<b>HIGH DIABETES MORTALITY (INDEX 115 OR OVER)</b>	
Merchants and storekeepers . . . . .	204
Tailors and other clothing workers . . . . .	185
Saloonkeepers and bartenders . . . . .	157
Railway enginemen and trainmen . . . . .	154
Electricians . . . . .	140
Store clerks and salesmen . . . . .	137
Watchmen and guards . . . . .	125
Clerks, bookkeepers and office assistants . . . . .	121
Stationary engineers and firemen . . . . .	118
<b>AVERAGE DIABETES MORTALITY (INDEX 86 TO 114)</b>	
Machinists . . . . .	107
Iron and steel-mill workers . . . . .	107
ALL OCCUPATIONS (EXCLUDING RETIRED) . . . . .	100
Railway track and yard workers . . . . .	97
Plumbers, gasfitters, and steamfitters . . . . .	96
Textile (except cordage, hemp, dyeing, and finishing) millworkers . . . . .	91
<b>LOW DIABETES MORTALITY (INDEX 85 OR LESS)</b>	
Teamsters and drivers . . . . .	84
Furniture and other woodworkers . . . . .	81
Farmers and farm laborers . . . . .	77
Laborers . . . . .	68
Janitors and building employees . . . . .	68
Painters, paperhangers, and varnishers . . . . .	61
Carpenters . . . . .	59
Coalminers (underground) . . . . .	51

\* Occupations with less than 15 deaths excluded except where the mortality is very high or low.

† For explanation of this term see original Ref. 37.

*The Effects of War and Economic Crises on Diabetes.* The period of the World War was marked by drastic declines in diabetes mortality. Three features of especial significance stand out in this War experience: (1) these declines were not immediate; (2) they did not end until 2 or 3 years after the close of the War; and (3) they were not limited to the fighting nations. In England, for example, diabetes rates actually increased in the early War years. In Germany, if we may take Berlin as typical, the declines in the first 2 years were no greater than pre-War fluctuations, and, likewise in France as represented in the data for Paris. Subsequently, the rates fell sharply, usually beginning in 1917, and continued to fall up to 1920. If we compare the 1914-1916 levels with those for 1917-1920, we find that in England, the decline amounted to 17%; Berlin, 42%; and Paris, 21%. Even in the United States which did not enter the War until 1917, the decline was 5%. Neutral countries experienced declines in diabetes mortality somewhat less drastic as, for example, 6% in Holland and 10% in Sweden and Switzerland.

These great changes in the diabetes death rates during and after the War are significant. To a limited extent, so far as the warring nations are concerned, part of this fall may have been fictitious. Because of the diversion of physicians into military service and the consequent restriction on medical care available to civilians many cases of diabetes were probably not diagnosed. Counter-balancing this situation in some degree, however, is the probability that known diabetics did not receive adequate care. This would tend to increase their death rate. These items certainly did not hold true for neutral countries in which the diabetes rates also fell. Both the warring nations of Europe and the neighboring neutral countries were subjected to sharply restricted food supplies and a consequent reduction in per capita food consumption. It is probable that this in part explains the fall in the rates during the War.

Economic crises might also be expected to result in sharp declines in diabetes mortality, because they are accompanied by drastic reductions in the incomes of large numbers of people. Examination of the data for the present century do not, however, show this effect in any marked degree. The crisis of 1907 is not reflected in the course of the diabetes death rate in this country or in England. During 1912-1915 the rate in this country continued to rise although there was a sharp decline in business. The year 1921 which witnessed a serious economic upheaval was marked by an increase in diabetes death rates almost everywhere. Again, since 1929, the rates from the disease have been going up in almost every country despite the severe world-wide depression. This result may represent the working of several forces. Depressions are usually accompanied by declines in commodity prices and, unless acute shortage exists, the prices of foodstuffs drop as rapidly as the rest. Conse-

quently, the fall in consumption of food is not as great as one would otherwise expect, particularly since there is a tendency for a greater proportion of the family income to be spent on food. Moreover, depressions actually bring improvement to the economic position of one large group—namely, those with relatively fixed incomes. Another factor in the situation is the neglect to secure proper medical attendance which results in some premature deaths of sufferers from the disease, and this also keeps the rate from falling for a time.

*Sugar Consumption in Relation to Diabetes.* Much has been written on this subject, but, as the earlier writings of one of us<sup>38</sup> have stated, the relationship is of doubtful validity. Table 11, largely reproduced from Mills<sup>39</sup> article, gives the facts on sugar consumption during 1923–1928 and the diabetes death rates in several countries in 1927. He concludes that no direct relationship between sugar consumption and diabetic deaths is shown. Some countries with a high sugar consumption (Hawaii, Argentina, Cuba) had a relatively low diabetic death rate, while some with a high rate from diabetes (Netherlands and the Union of South Africa) had a low sugar consumption. Of the 13 countries highest in consumption of sugar, however, 11 were among the 13 highest in the death rate from diabetes.

TABLE 11.—DIABETES MORTALITY AND SUGAR CONSUMPTION IN VARIOUS COUNTRIES. 1923–1928.

Country.	Diabetes death rate per 100,000 in 1927.	Sugar consumption—kilograms per capita.				
		1927–1928.	1926–1927.	1925–1926.	1924–1925.	1923–1924.
United States . . . .	17.5	49.6	51.3	52.2	52.5	49.2
Netherlands . . . .	16.3	30.0	26.3	28.7	28.6	26.8
New Zealand . . . .	13.7	29.5	34.1	37.7	50.0	46.0
Belgium . . . . .	13.3	26.4	24.4	24.6	24.9	21.9
Australia . . . . .	13.1	58.0	58.2	58.3	58.7	59.9
Denmark . . . . .	13.0	51.7	48.6	53.8	49.7	48.2
England and Wales* .	12.6	44.8	41.1	41.2	40.6	38.4
Sweden . . . . .	12.0	37.7	35.9	37.0	37.1	33.8
Canada . . . . .	11.1	40.8	40.3	41.4	41.9	40.0
Norway . . . . .	10.5	31.4	30.4	27.0	28.0	23.0
Switzerland . . . .	10.3	42.5	34.3	39.7	36.3	36.8
Spain . . . . .	9.3	12.2	11.9	10.8	10.8	10.5
Hawaii . . . . .	8.5	55.1	55.0	55.0	54.7	54.4
Italy . . . . .	7.1	9.1	8.9	8.9	8.4	8.7
Czechoslovakia . . .	6.3	27.0	25.7	28.6	27.6	25.8
Cuba . . . . .	5.1†	44.3	44.9	44.0	35.6	33.1
Chile . . . . .	3.5	....	....	....	20.2	25.0
Japan . . . . .	3.5	....	12.7	12.4	....	....

\* Sugar consumption for Great Britain.

† 1926.

Also no constant relationship between sugar consumption and the diabetic death rate was found. In some with a steady increase in sugar consumption for many years, there has been a recent decline in diabetic deaths (*e. g.*, Norway and Australia). New Zealand with

a marked decline in sugar consumption showed little change in the diabetic death rate. Hawaii, with a steady high consumption of sugar showed a considerable increase in diabetes. In the United States, the consumption of sugar has been constant for several years, but diabetes is increasing.

The authors agree with Mills that the increase in sugar consumption is not the cause of the increase in the diabetes death rate. The consumption of sugar may, however, be a rough index of nutrition or the total food consumed and to that extent accounts for whatever degree of association there is between sugar consumption and diabetes mortality. For in northern countries where sugar consumption is high, food requirements are higher than in warmer climates, and the greater use of sugar in the former is undoubtedly due to its cheapness as a source of energy for body needs. In some cases, of course, this does not hold, notably for countries which specialize in the production of sugar, namely, Cuba, Puerto Rico, Hawaii and the Philippines.

**Summary.** Consideration of the available material on incidence of diabetes and the factors underlying variations in its frequency reveals these significant facts.

1. The number of known diabetics in this country is probably between 300,000 and 400,000. This estimate takes into account current diabetes mortality, the duration of life of diabetics, and the incidence of diabetes recorded in the various sickness surveys.

2. A large increase in the incidence of diabetes is indicated by comparison of earlier surveys with recent ones, and also by hospital statistics.

3. The incidence of diabetes abroad seems to be lower than in this country. Here the case incidence is about  $2\frac{1}{2}$  to 3 per M, compared to  $1\frac{1}{2}$  to  $2\frac{1}{2}$  in the various countries of western Europe. The number of diabetics in Germany is estimated as 100,000-150,000 and in England as 50,000-75,000. Estimates for the other large countries cannot be made, because data necessary for computing them are not available.

4. Mortality statistics show that  $2\frac{1}{2}$  million persons (2.08% of the present population) may be expected ultimately to succumb to the disease. The chances of eventually dying from diabetes are nearly twice as high for females as for males, and are higher for white persons than colored persons.

5. Diabetes is more prevalent and seems to be increasing faster in urban areas than in rural ones.

6. In this country, the northeastern states have a much higher diabetes death rate than those in the south. Average rates prevail in the middle west and on the Pacific Coast. This variation is greater in the rural than in the urban population.

7. In Europe diabetes rates are relatively high in the north and west and low in the south.

8. The Teutonic peoples suffer more frequently from diabetes than the Latins. The data on Czechoslovakia, if typical, indicate a low diabetes rate among the Slavic peoples. National and racial tendencies in this country conform largely to those abroad, except among the Irish, who, in Ireland, have a very low diabetes rate, but a high rate in this country.

9. Recent studies of mortality in New York bring out clearly the excessive frequency of diabetes in Jews and confirm earlier clinical observations. This finding does not seem to apply to young Jews. Among the older ones, the incidence is probably  $1\frac{1}{2}$  to twice the average.

10. Diabetes is more frequent in the higher than in the lower social classes.

11. The employing and professional groups tend to have high diabetes rates. This is also true of those who sell or serve food and drink. Diabetes is least frequently found in persons engaging in occupations requiring hard manual labor.

12. Long sustained wars result in decreases in the diabetes rate, largely as a consequence of the reduction of food supplies available to civilians. For a variety of reasons the effect of economic crises is not altogether clear-cut, but in any case, it is less direct and less influential than the effect of war conditions.

13. Sugar consumption in itself is not an important factor in the diabetes rate, nor in the increasing incidence of the disease.

In the judgment of the authors the several external factors influencing the incidence of diabetes, which are the subject of the present article, depend upon a very few basic forces. We shall next discuss what these are and the way in which they operate.

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## THE EFFECT OF ADRENALIN ON THE ALIMENTARY LIPEMIA OF DIABETICS.\*

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THE utilization of ingested fat in health and disease and what regulates this utilization has never been satisfactorily explained. Numerous investigators have demonstrated the rôle of adrenalin in carbohydrate metabolism and its antagonistic action to insulin. As insulin lowers blood lipoids,<sup>1, 2, 3, 4, 5, 6, 7</sup> as well as blood sugar,

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it is important to determine whether adrenalin, which causes an increase in blood sugar, would cause an increase in blood lipoids, and whether adrenalin would counteract the action of insulin on lipemia if the two hormones exerted their influence simultaneously.

With a fat method essentially that of Stewart and White,<sup>8</sup> Himwich and Spiers<sup>9</sup> demonstrated a parallel rise of blood sugar and blood fats following the injection of adrenalin into animals, also an apparent equalizing or counteracting force of insulin on this adrenalin effect. Then Himwich and Fulton<sup>10</sup> showed that after noxious stimulation of animals calculated to cause emotional excitation and stress thereby presumably increasing their secretion of adrenalin, there was a rise in the blood fats as well as the blood sugar. Koskoff and Dusser de Barenne,<sup>11</sup> using the Stewart and White method, found that stimulation of the central end of the sciatic nerve in an anesthetized cat caused a reflex hyperlipemia. These findings Long and Venning<sup>12, 13</sup> disputed because they discovered in the Stewart and White method and its modification two sources of error: (1) During the saponification of alcohol-ether extract of plasma the glucose present breaks down the complex organic acids which are titrated as fatty acids; (2) phosphoric acid is liberated from the hydrolysis of phospholipoids and is titrated as fatty acid. Thus the alleged rise in blood fats after adrenalin was due to the increased blood sugar in the faulty method employed. With the Stoddard and Drury<sup>14</sup> method which is free from these two objections, Long and Venning found no increase in blood fats after adrenalin injections, whereas the same samples of blood tested with the Stewart-White method showed a decided "increase in lipoids."

Page and Pasternak<sup>15</sup> gave normal dogs 0.3 mg. of adrenalin every 15 minutes and 4 hours after the first injection noted a diminution of cholesterol, phosphorus, fatty acids and total fat in serum, an increase of the same in the liver, and a reduction of the same in the kidneys. There was also found a reduction of phosphatids with an increase of cholesterol in the brain and in the heart and slight reduction of the fatty acids (unsaturated), a reduction of phosphatid and cholesterol and a slight reduction of the unsaturated fats. In dogs with hyperlipemia they obtained similar findings. They concluded that although the mechanisms of insulin and adrenalin actions were different, their effects on blood fat were the same.

Using the Bang method Fleisch<sup>16</sup> found that intravenous injections of 0.1 to 1 mg. of adrenalin in animals produced during 24 hours a sinking of the blood-fat content of 17 to 30 per cent. Large doses of 3 to 6 mg. subcutaneously caused in the first or second day an intensive increase in the blood fat (2 to 4 fold). This increase ordinarily passed in 24 hours. Very small doses up to 0.1 had no certain effect. Raab<sup>17</sup> found that small doses of adrenalin (0.1 to 1 mg.) caused a sinking of the blood-fats. Bornstren and Müller<sup>18</sup>

demonstrated a strong reduction of total and neutral fat in normal dogs after adrenalin.

Analyzing the findings of these different investigators it is noted that although Long and Venning found no change in blood fats after adrenalin and Fleisch obtained an increase after a massive dose, the findings of Page and Pasternak, of Fleisch, of Raab, and of Bornstren and Müller are in agreement, namely, after small or moderate doses of adrenalin there is a decrease in blood fats. As a step toward the ultimate understanding of the complexities of fat metabolism this fact is significant. It would appear, however, that in a problem in which utilization of foodstuff (fat) is a paramount issue, the obvious approach would have been the study of subjects in the absorptive stage.

**Method.** Accordingly we selected 11 diabetic patients, all of whom were well controlled on a diabetic regimen; that is, they were aglycosuric or nearly so, and clinically well. After a 15-hour fast, a specimen of blood was obtained from each patient and 100 grams of cotton seed oil was administered orally. Blood samples were taken at 3, 6 and 9 hours after the oil drink. Total lipoids were determined by the method of Ruckert.<sup>19</sup> This ingenious method is simple and accurate and has been checked against the more elaborate, time-consuming methods. Its principle is the same as the Gerber milk-fat method and it is free from the sources of error that were pointed out for the Stewart and White method. Emulsions of known quantities of fat as well as various dilutions of fat containing liquids are recovered with great accuracy.

Very briefly the technique for performing the test is as follows: A small quantity of serum (0.15 cc.) is drawn up into a specially constructed lipokrit pipette and mixed with a mixture of sulphuric acid (70 per cent, Sp. Gr. 1.616) which contains methylene blue, and amyl alcohol which contains anilin yellow. The proteins are hydrolyzed by the sulphuric acid and changed from colloidal state to a state of molecular dispersion. The fat is liberated and then dissolved by the amyl alcohol. The anilin yellow colors the dissolved fat a brilliant yellow which after centrifugalization collects above and is measured volumetrically on a graduated scale. The phosphatids dissolve in the alcoholic-sulphuric acid mixture and are re-precipitated as fatty acids. This fatty acid fraction rises gradually and in 24 hours it also is read off the graduated scale. The difference between the total fats and the neutral fat value equals the fatty acid fraction of the phosphatid, from which is readily computed the amount of phosphatid. For a detailed description of this method in English, see the article of Douglas Collins.<sup>20</sup> This investigator did not follow Ruckert's directions exactly as we did. He disregarded the immediate reading of neutral fat, and calculated his results for volume per cent instead of milligrams of total fat. The final step of computing the phosphatid value from its fatty acid fraction was omitted.

**Results.** The results of these fat absorption curves are recorded in Table 1, Columns 1A, 2A, 3A, 4A, 5A, 6A, 7A, 8A, 9A, 10A and 11A. With the exception of Cases 5 and 9 which continued to show a rise even at the 9th hour, the peak of absorption was reached at the 6th hour and by the 9th hour the lipid values were approaching the fasting values. Ten days later these 11 patients were again given 100 grams of oil after fasting 15 hours. Blood specimens were taken just before the oil was drunk, 3, 6 and 9 hours after. At 2½,

TABLE 1.—TOTAL BLOOD (SERUM) FATS OF 11 DIABETIC PATIENTS EXPRESSED IN MILLIGRAMS PER 100 CC. BEFORE 3, 6 AND 9 HOURS AFTER THE INGESTION OF 100 GRAMS OF COTTONSEED OIL (COLUMN A), AND (COLUMN B) 10 DAYS LATER WITH 1 MG. OF ADRENALIN (SUBCUTANEOUSLY).

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PER 100 MG. OF ADRENALIN.

11

		1		2		3		4		5		6		7		8		9		10		11	
		A		A		B		A		B		A		B		A		B		A		B	
Case No.																							
Fasting . . . .		704	677	351	798	613	798	735	731	991	991	991	911	591	651	918	885	707	845	517	631	731	527
100 gm. oil per os: 2½ hrs. later . .		..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.
3 hrs. later . .		863	818	607	766	871	918	951	862	1142	1197	998	966	774	798	1149	1016	951	925	778	886	838	903.
5½ hrs. later . .		..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.
6 hrs. later . .		1579	758	775	965	1231	918	1111	1006	1150	1165	1030	882	846	743	1492	1181	1046	848	831	766	911	815
8½ hrs. later . .		..	..	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	..	..	..	1 cc. adr.	814
9 hrs. later . .		1196	..	656	878	1098	894	1011	870	1249	925	925	694	814	702	1430	1189	1085	531	758	831	814	

5½ and 8½ hours after the ingestion of the oil 1 mg. (1 cc.) of adrenalin was given subcutaneously (total dosage 3 mg. in 6 hours). The effect of the adrenalin on the absorption curves was striking (see Table 1, Columns 1B, 2B, 3B, 4B, 5B, 6B, 7B, 8B, 9B, 10B and 11B). In all except one (Case 11), who was the only patient in the group taking a high-fat diet, the adrenalin caused a decided lowering of the blood lipoids as compared with the values for the lipoids when no adrenalin was given. This one exception (Case 11) was a young woman who had lost much weight, with suspected pulmonary tuberculosis, who in the adrenalin experiment became nauseated, developed tachycardia, experienced substernal pain, vertigo and was greatly distressed. Thus she should perhaps be excluded from this group, which consisted of healthy individuals on low-fat diets. Although all of the other patients experienced the physiologic effects of the adrenalin and commented on "a strange feeling, nervousness, dizziness, heart consciousness," none except Case 11 was distressed.

**Discussion.** It is reasonable to suppose that there is a hormonal influence on, if not regulation of, fat metabolism. So complex is fat metabolism that its exact mechanism has never been elucidated. The control of carbohydrate metabolism is better understood, and therefore the substances (adrenalin and insulin) which have been shown to influence carbohydrate utilization should be studied carefully in their effects on fat utilization. Oxidation of fat after a certain point requires simultaneous combustion of glucose. However, a hard and fast relationship of carbohydrate and fat content of the blood has never been demonstrated. It is known that carbohydrate is converted into fat and it is believed that fat may be converted into carbohydrate, but this mechanism is obscure. Indeed the form in which fat is absorbed is unknown. There has been much speculation concerning the rôle of hormones in fat metabolism. After studying the effects of pituitrin, adrenalin and other substances on fat metabolism, Raab<sup>17</sup> concluded that there was a regulated utilization of fat through adrenalin and insulin for the purpose of carbohydrate replacement maintaining the tissues with sugar. Cori, Cori and Buckwald<sup>21</sup> have stressed the important rôle played by the decreased utilization of blood sugar in epinephrin hyperglycemia. If a decrease in the utilization of blood sugar did occur after the injection of adrenalin in the patients observed, the lowering of the blood fats was probably due to the immediate utilization of the fat by the tissues. Had the experiment been continued over a longer period of time, there might have been a secondary rise of the blood fats with ketonemia, due to incomplete combustion of the fat. This suggests a possibility that the alternate use of adrenalin and insulin with high carbohydrate, high-fat diet might prove a valuable adjunct in convalescent and malnourished non-diabetic patients when optimum food utilization is desired.

**Summary and Conclusions.** 1. The administration of adrenalin in dosage sufficient to produce physiologic response causes a lowering of the increasing blood fats in the alimentary lipemia of diabetes mellitus.

2. This fact is significant as additional evidence supportive of the view that adrenalin has a direct regulatory effect on fat metabolism.

We wish to express our appreciation to Dr. I. I. Lemann, Professor of Clinical Medicine, for his advice and cooperation and the permission to use his patients for this study.

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## THE DISTRIBUTION OF SUGAR AND CHLORID IN THE BLOOD OF DIABETIC INDIVIDUALS.

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THE distribution in the corpuscles and the serum of the different components of whole blood has been studied by many investigators. Although the concentrations of the various constituents in the blood may be strikingly different in the corpuscles and in the serum, nevertheless, from freezing-point studies<sup>1</sup> it would appear that the cells

are in osmotic equilibrium with the serum. The sum of the osmotically active electrolytes in the corpuscles has been shown to equal the sum of the osmotically active electrolytes in the serum when calculated on a water basis, although the concentrations of the individual ions in the corpuscles and the serum are not equal. The non-electrolytes of small molecular size theoretically should be equally distributed and freely diffusible throughout both cells and serum. Concerning the various non-electrolytes there are data in the literature suggesting that glucose may not be freely diffusible and that its distribution between corpuscles and serum may be abnormal in pathologic conditions such as diabetes mellitus.

Chlorid has been regarded as one of the most mobile of the anions present in the blood, because of the readiness with which the concentration of chlorid can be reduced to make way for other anions. It has been suggested that changes in the concentration of  $\text{BCl}$  may serve as a regulator of the osmotic pressure for variations in the concentration of non-electrolytes. Herrick<sup>2</sup> has demonstrated an inverse relationship between chlorid and glucose in the whole blood. Ni<sup>3</sup> has found similar relationships in the blood of depancreatized dogs. Gram<sup>4</sup> believed that there was a reduction in chlorid concentration in the course of chronic nephritis which occurred as a compensation for the retention of non-protein nitrogenous substances. Sunderman, Austin and Williams<sup>5</sup> found an inverse relationship between glucose and chlorid concentration after the administration of insulin to diabetic patients, although freezing-point studies indicated that the reduction in glucose was not entirely compensated for osmotically by the increase in the chlorids.

Somogyi<sup>6</sup> reviewed the literature on the distribution of sugar in the blood in 1928. Certain earlier investigators had concluded from their analyses of cells washed in physiologic salt solution that corpuscles contained no fermentable sugar. Later investigators, by measuring the total reducing substances in the cells and serum, arrived at the view generally accepted until 1928 that there was a nearly equal distribution of blood sugar between the corpuscles and plasma, the ratio  $\frac{\text{corpuscle sugar}}{\text{plasma sugar}}$  (concentration by volume) being

on the average 1.1. Somogyi demonstrated that there was approximately 5 times as much non-fermentable reducing substance in the corpuscles as in the serum and that when the non-fermentable reducing substances were subtracted the ratio of sugar in the corpuscles to sugar in the serum was less than 1 (the average being 0.77) and was approximately the same for diabetic individuals as for non-diabetic individuals. John<sup>7</sup> found the ratio of  $\frac{\text{corpuscle sugar}}{\text{plasma sugar}}$  (concentration by volume) to be lower for diabetic subjects than for non-diabetic subjects. His measurements apparently did not take into account the correction for non-fermentable reducing

substances. On the other hand Folin and Svedberg<sup>8</sup> found the distribution ratio to be higher in diabetic than in non-diabetic individuals. They found a ratio  $\frac{\text{corpuscle sugar}}{\text{plasma sugar}}$  (concentration by volume) of approximately 0.60 for non-diabetic and 0.69 for diabetic individuals. Bose<sup>9</sup> recently reported that the distribution ratio  $\frac{\text{corpuscle sugar}}{\text{plasma sugar}}$  (concentration by volume) was lower in diabetic than in normal subjects. He considered the measurement of this ratio to be of prognostic value, the lower the distribution ratio the more severe the diabetes.

Foshay<sup>10</sup> found that the administration of insulin in diabetic patients altered the distribution of sugar in the corpuscles and in the plasma. He considered the finding of a low ratio an indication of approaching insulin shock. Trimble and Maddock<sup>11</sup> failed to confirm this finding. They found no change in the distribution ratio after insulin administration. Spannuth and Power<sup>12</sup> found the distribution ratio for glucose to be about the same in the diabetic and in the non-diabetic subject. After the administration of glucose they found the ratio to be unchanged in the normal person but to be decreased in the diabetic individual.

In consideration of these conflicting views, the present study, designed to measure the distribution of glucose and chlorid in the corpuscles and serum of normal individuals and of individuals suffering from diabetes mellitus, seemed desirable.

In all of the observations cited with respect to glucose the measurement of the glucose has been expressed in terms of volume of solution. Since in measurement of osmotic pressure results more concordant with theory are obtained if the concentration of solute is expressed in terms of the volume of solvent at its maximum density rather than in terms of volume of solution, the results of our measurements of glucose and chlorid have been calculated on a water basis. During the process of this investigation an article appeared by MacKay<sup>13</sup> in which when similar calculations were made, glucose was found to be freely diffusible and equally distributed in the water of the corpuscles and the plasma of heparinized blood. His data included the analysis of blood obtained from 2 diabetic patients.

Mosonyi<sup>14</sup> measured the partition of sugar in the blood following the ingestion of glucose and the administration of insulin respectively in dogs. Although his data did not include analyses of the water content of the corpuscles or serum, nevertheless, when reasonable approximations were made as to the water content of the corpuscles and serum, Mosonyi obtained results which in certain instances were incompatible with the observations of MacKay of an equal distribution of glucose in the water of the cells and the water of the serum. In fact Mosonyi found the concentrations of

glucose by volume to be higher in the cells than in the serum in 6 of his analyses.

**Materials and Methods.** Our studies were made on blood obtained from 5 normal individuals attached to the laboratory and from 22 patients suffering from diabetes mellitus attending the metabolic clinic of the Pennsylvania Hospital. After an overnight fast, venous blood was collected directly under oil without stasis. Samples were defibrinated and divided into two portions, both of which were centrifuged. The serum was removed from one portion and the other portion was stirred with a glass rod to insure an even remixture of the serum and the cells. Samples of the serum and whole defibrinated blood were analyzed for glucose within 20 minutes after

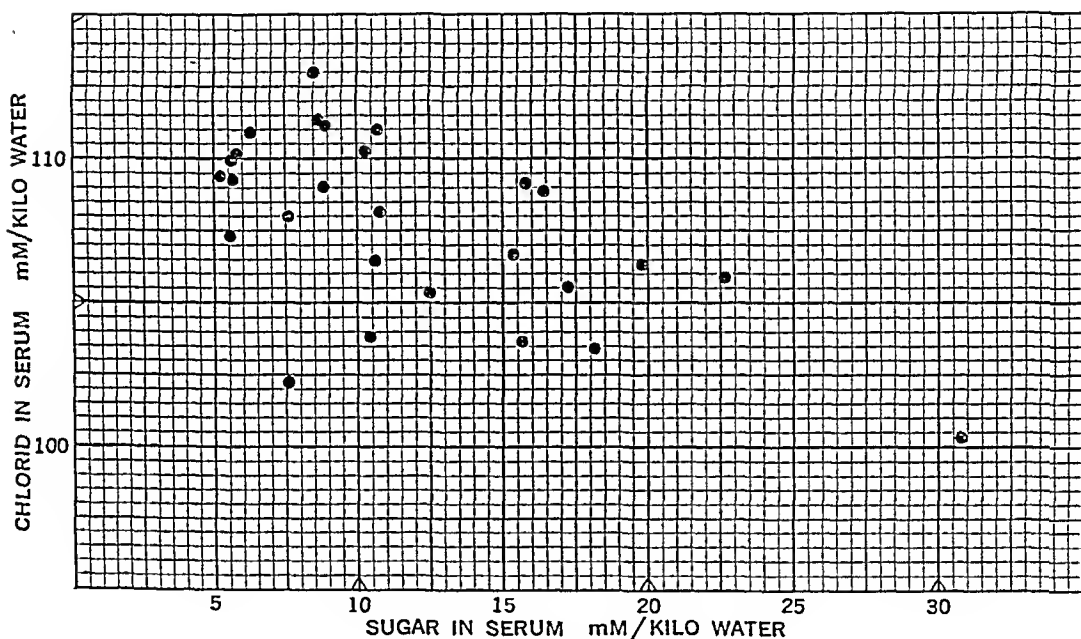


FIG. 1.—Sugar and chlorid in serum.

obtaining the specimens. The glucose measurements were made according to the Benedict method.<sup>15</sup> The other methods used in this study have been described in previous papers.

**Calculations.** For the calculation of the concentration of glucose and chlorid in the cells and the serum the following formulæ were used:

Symbols: X = concentration in grams of either glucose or chlorid

R = dry residue in grams

G = specific gravity

c, s, w. b. = cells, serum and whole blood respectively

% = percentage of cells or serum by volume



( ) = concentration in grams per liter of serum or cells

[ ] = concentration in grams per kilogram of water

{ } = concentration in grams per kilogram of serum or cells

The concentration of sugar or chlorid per kilogram of water in serum:

$$(1) [X]_s = \frac{(X)_s \times 1000}{G_s (1000 - \{R\}_s)}$$

The concentration of sugar or chlorid per kilogram of water in cells:

$$(2) [X]_c = \frac{(X)_c \times 1000}{G_c (1000 - \{R\}_c)}$$

where

$$(2a) (X)_c = \frac{100 (X)_{w. b.} - \% s (X)_s}{\% c}$$

$$(2b) G_c = \frac{100 G_{w. b.} - \% s G_s}{\% c}$$

$$(2c) (R)_c = \frac{100 \{R\}_{w. b.} \times G_{w. b.} - \% s \{R\} G_s}{\% c}$$

$$(2d) \{R\}_c = \frac{(R)_c}{G_c}$$

**Results.** The results of the analysis of the bloods of 22 diabetic patients and 5 normal subjects are presented in Table 1. When the concentrations of glucose were calculated on a water basis the average ratio  $\frac{\text{corpuscle sugar}}{\text{serum sugar}}$  was found to be  $1.023 \pm 0.0088$  (S. E.) for the diabetic patients and  $1.035 \pm 0.025$  (S. E.) for the normal individuals.

The ratio of  $\frac{\text{corpuscle chlorid}}{\text{serum chlorid}}$  was found to average  $0.683 \pm 0.004$  (S. E.) for the diabetic bloods and  $0.672 \pm 0.017$  (S. E.) for the normal bloods. When the ratio found in the diabetic blood was corrected to 100-percent oxygenation, the corrected ratio was 0.66.\* The pH of the serum and of the whole blood was measured by means of the glass electrode in 9 of the specimens obtained from diabetic patients. Since all of the measurements fell within relatively narrow limits (0.13 of pH), the average pH (7.464) of the 9 measurements was used as the average of the entire series. The degree of oxygenu-

\* The correction was made by the formula

$$C = 0.1 (\text{pHs} - 6.6) \frac{\text{reduced Hb}}{\text{total Hb}}$$

where c is the amount by which the observed ratios must be decreased to give the ratio for completely oxygenated blood (16).

TABLE 1.—RESULTS OF ANALYSES. DIABETIC INDIVIDUALS.

Case.	Sugar		Chlorid		Cell volume.	Sp. Gr.		Solids		Ratio		Ratio Corp. Cl. Serum Cl.
	Corp.	mM/Kg of water.	Corp.	mM/Kg of water.		Corp.	20°/20°	Corp.	Gm/Kg of corp.	Corp. sugar.	Water basis.	
10377	10.25	10.71	73.4	108.1	42.2	1.0924	1.0286		329.09	0.96	0.68	
63859	7.85	7.57	71.2	102.3	47.8	1.0944	1.0296		337.26	1.04	0.70	
1765	15.44	15.61	69.5	103.6	44.0	1.0939	1.0280		328.54	0.99	0.67	
18761	9.99	10.67	70.2	106.5	43.3	1.0915	1.0272		318.84	0.93	0.66	
252	8.38	8.52	77.0	112.9	41.0	1.0839	1.0260		298.58	0.98	0.68	
61563	12.13	11.76	73.9	110.9	39.4	1.0909	1.0290		320.88	1.03	0.67	
27131	18.38	18.13	72.1	103.4	43.0	1.0851	1.0276		292.35	1.01	0.70	
61973	12.70	12.48	73.3	105.4	45.2	1.0956	1.0273		338.50	1.02	0.70	
49214 B	10.09	10.36	69.1	110.2	39.3	1.0980	1.0271		327.15	0.98	0.63	
26900 U. H.	9.67	8.88	76.5	109.0	42.4	1.0958	1.0281		358.57	1.09	0.70	
26261	18.25	17.31	72.1	105.5	42.6	1.0939	1.0266		330.04	1.05	0.68	
2974 B	9.30	8.91	84.3	111.1	40.6	1.1062	1.0261		376.13	1.04	0.76	
279	23.11	22.71	69.0	105.8	46.0	1.0926	1.0278		324.24	1.02	0.65	
82062	16.22	15.32	68.7	106.7	48.2	1.0893	1.0287		323.57	1.06	0.64	
37969	8.13	7.60	74.8	107.9	44.8	1.0953	1.0263		337.93	1.07	0.69	
62155	6.71	6.43	72.9	110.8	43.3	1.0988	1.0308		354.32	1.04	0.66	
2771 A	16.46	16.33	86.1	108.8	49.0	1.0922	1.0301		316.6	1.01	0.79	
2041 A	15.89	15.94	74.5	108.6	50.1	1.0912	1.0249		322.64	1.00	0.69	
39579	9.39	11.4	78.5	111.4	44.6	1.0980	1.0301		334.1	1.08	0.71	
15777	10.92	10.49	60.6	103.8	37.5	1.0968	1.0282		318.8	1.04	0.58	
2041 A	20.61	19.61	71.1	106.4	51.2	1.0930	1.0275		330.6	1.05	0.67	
4353 B	31.24	30.79	72.4	100.4	43.2	1.0940	1.0281		339.67	1.02	0.72	

## NORMAL INDIVIDUALS.

100	5.55	5.72	72.0	109.6	46.3	1.0981	1.0265		349.75	0.97	0.66	
101	5.74	5.79	67.5	110.0	45.0	1.0958	1.0263		345.5	0.99	0.61	
102	6.30	5.74	71.8	107.3	46.3	1.0961	1.0283		379.3	1.10	0.70	
103	5.95	5.76	75.6	109.2	52.0	1.0955	1.0280		372.2	1.03	0.69	
104	6.35	5.80	76.5	109.1	50.0	1.0924	1.0279		333.76	1.08	0.70	

tion of the venous blood was assumed to be approximately 75 per cent saturated. Any moderate variation from this figure would not change this correction to any significant degree.

While there appeared to be no definite linear relationship between the level of glucose and the level of chlorid from subject to subject in either whole blood, corpuscles, or serum, calculated on either a liter or a water basis, nevertheless, in general there was a tendency for the high values of sugar to be associated with the low values of chlorid and *vice versa*. In Fig. 1 we have plotted the values for glucose and chlorid of the serum on a water basis, demonstrating the scattering observed.

**Discussion.** Peters and van Slyke<sup>18</sup> have pointed out that it was doubtful at the time of their publication whether the distribution of chlorid between cells and serum could be explained purely on the basis of the Donnan theory because of the deviation of analytical data from the calculated values. The factor for the chlorid ratio is about 0.8 to 0.9 times that for the bicarbonate. The presence of an organic chlorid which might account for this discrepancy has never been demonstrated in blood. From recent experiments demonstrating the occlusion of chlorid by fat<sup>19</sup> we suggest the possibility that a fraction of chlorid in the cells might be held by the lipoids and as such be incapable of diffusion.

When corrected for changes in the CO<sub>2</sub> and oxygen tension, the ratio  $\frac{\text{corpuscle chlorid}}{\text{serum chlorid}}$  does not appear to deviate in a series of pathologic states studied from the normal, as shown in the following table:

	pH.	$\frac{\text{Clc}}{\text{r Cls}}$
Hastings <i>et al.</i>		
Normal . . . . .	7.38	0.689
Nephritis . . . . .	7.35	0.700
Pneumonia . . . . .	7.42	0.674
	pH.	$\frac{\text{Clc}}{\text{r Cls}}$
Muntwyler <i>et al.</i>		
Various conditions . . . . .	7.42	0.669
Williams and Sunderman		
Diabetics . . . . .	7.46	0.660

When calculated on a water basis, sugar in the blood appears to be freely diffusible between the corpuscles and serum in the blood of normal subjects and of patients suffering from diabetes mellitus. Benedict reported that his method for the measurement of glucose included about 3 to 5 mg. per cent of non-fermentable reducing substances. Since it is generally believed that the cells contain the greater part of these substances this difference may account for the fact that our ratio of  $\frac{\text{corpuscle sugar}}{\text{serum sugar}}$  is slightly above unity.

**Conclusions.** The distribution of glucose and chlorid between the corpuscles and the serum has been studied in the blood obtained from diabetic patients and normal patients. In both the diabetic and normal blood the glucose was found to be approximately equally distributed throughout the water of the corpuscles and the serum. This is in agreement with the findings of MacKay.

The distribution of the chlorid in the water of the cells and the water of the serum of diabetic blood did not differ essentially from the distribution found by other investigators in normal and pathologic blood.

No consistent relationship between the level of glucose and the level of chlorid in the whole blood, corpuscles, or serum was observed.

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## STUDIES ON TRANSIENT VENTRICULAR FIBRILLATION.

### I. OBSERVATIONS ON THE ALTERATIONS IN THE RHYTHM OF THE HEART PRECEDING SYNCOPAL SEIZURES IN A PATIENT WITH NORMAL SINUS RHYTHM.

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THERE are exceedingly few observations on the disturbances in the rhythm of the heart which precede the onset of spontaneously

developed transient ventricular fibrillation in man. A careful examination of the electrocardiograms of the few instances of ventricular fibrillation reported in the literature since the introduction of the electrocardiograph reveals a meager knowledge of this mechanism; yet, experiences at the Montefiore Hospital within the past few years with such patients lead to the belief that ventricular fibrillation as a cause of recurrent syncopal attacks is, in all probability, much more commonly the cause of Stokes-Adams seizures than has been suspected hitherto.<sup>1,2,3</sup>

It is the purpose of this and similar studies that follow it, to describe the natural course of syncopal attacks due to ventricular fibrillation as they occur in man, and to point out how this mechanism is ushered in, and in what respects these pre-fibrillatory periods are totally different from any other type of ventricular irregularity encountered in practice. Only certain features of these pre-fibrillatory irregularities are pathognomonic for ventricular fibrillation.

The sequential disturbances of normal sinus rhythm preceding syncopal attacks are delineated in the following observations:

**Case Report.**—E. M., a boy, aged 17, was transferred to Montefiore Hospital from the Neurological Institute on December 20, 1932, and died on January 18, 1933.

He was perfectly well until 2 years before his admission to the hospital, when he contracted a "severe head cold" which subsided under local treatment. In November, 1932, he complained again of a "severe head cold" which was accompanied within 2 days by fever, occasional cough and diarrhea. On the morning of November 21, 1932, he noticed that his toes felt numb. On the same afternoon he found that his legs were weak and he was unable to void or move his bowels. On the following day the power in his legs became progressively weaker. Four days after the onset of his illness, he had lost all power in his legs and he observed a distinct difference in the temperature of his bath when he compared sensations between the upper and lower extremities. At this time he had to be catheterized because he was unable to void and from then on his bladder was irrigated once a day.

*Physical examination* on admission to Montefiore Hospital revealed an undernourished, brown-skinned youth who was comparatively free from distress. He was lying flat in bed. His respirations were 22 per minute. His heart rate averaged 92 beats per minute and the rhythm was regular. His temperature ranged between 98° and 101° F. There were 2 large ecchymotic areas over his sacrum and heels and there were several decubitus ulcers on his back. His eye grounds revealed temporal pallor in both disks. The apical impulse of the heart was in the 5th intercostal space within the midclavicular line. The heart sounds were of good quality. There were no murmurs. The lung fields were clear. The liver and spleen were not palpable. The legs showed no edema. There was a flaccid paraplegia with practically all reflexes absent except the right knee jerk, which was very feeble. A definite sensory level could be demonstrated in the region of the 7th dorsal vertebra.

The Wassermann reaction of the blood and spinal fluid was negative and the cerebrospinal fluid was clear, colorless, and not under pressure. The urine showed a considerable number of pus cells and there was moderate secondary anemia.

*Course During Stay in Hospital.* During his stay in the hospital, the boy's fever persisted. He was first seen during a seizure of unconsciousness

on the morning of January 16, 1933. His breathing was stertorous and difficult, his head and eyes were turned to one side, and there were mild tonic convulsions of his upper extremities. Two or 3 minutes after this episode the breathing returned to normal but he could not respond when addressed. He attempted to turn on his right side, closed his eyes and again had a mild "attack" of loss of consciousness, with stertorous breathing, extension of his head backward and to the side and deviation of his eyes to the right. Atonic contractions of his upper limbs were noted to follow, and during this episode the heart sounds were inaudible and his pulses were not palpable.

The eye grounds as observed by Dr. M. M. Abeles were unusually interesting at this time. During the collapse of the circulation when the heart sounds were inaudible and the blood pressure could not be recorded, the blood stream in the retinal vessels appeared fragmented. Some of the retinal veins had lost their contour completely and could be recognized only when "spurts" of blood corpuscles would flow through them when the heart beat again. As soon as the boy's pulse became palpable following an effectual ventricular contraction, all of the retinal vessels could be outlined.

Because of the increasing frequency of these recurrent periods of unconsciousness and on the assumption that these episodes were due to arrest of the circulation as a result of stoppage of the ventricles, an attempt was made to inject 0.5 cc. of a 1:1000 solution of adrenalin directly into the heart during a long seizure of unconsciousness. Immediately after the injection the boy became extremely restless. An occasional pulse beat came through at the wrist but there was a sudden tonic closure of the lower jaw and there were innumerable clonic convulsions of all of his limbs with marked frothing at the mouth and very forced difficult breathing, finally ending in apnea and Cheyne-Stokes respirations with the boy losing total consciousness and becoming comatose.

For the next 5 hours he was in a state resembling "status epilepticus." The pupils were widely dilated and fixed to light. The eye movements were in a vertical plane only. There was bilateral ankle clonus. There were tonic contractions of the muscles of the body with rigidity simulating "decerebrate" rigidity. In addition there were innumerable convulsions. The heart rhythm during this time was reported as being totally irregular with a pulse deficit, resembling the rhythm of auricular fibrillation with a very rapid ventricular rate.

On the following morning, January 17, 1933, the patient was still confused and dull although he no longer exhibited convulsive movements. At 1.00 P.M. of that day his pulse and heart rhythm were regular and averaged 110 beats per minute. When seen by us he spoke more clearly, and later as he was watched during the day his heart rate was noted to be rapid and irregular again and interrupted by a bigeminy. This arrhythmia alternated with long periods of regular rhythm and a ventricular rate of 110 beats per minute.

A hyperresonant note over the left half of his chest with displacement of his heart to the right was noted for the first time on this day. This was diagnosed and confirmed by radiograms to be due to air in the left pleural cavity following the attempt to inject adrenalin in the heart cavities on the previous day, when the absence of the boy's pulse was attributed to "ventricular standstill."

On January 18, 1933, the boy suffered from complete amnesia for several hours and still continued to have recurrent seizures of unconsciousness. On the morning of that day, however, the cerebral accidents were considered for the first time to be of cardiac origin and repeated electrocardiograms taken over long periods and correlated with his clinical manifestations during syncopal seizures revealed these attacks to be due to transient ventricular fibrillation.

He died in a long seizure of ventricular fibrillation which started with loss of consciousness and stertorous breathing and ended in apnea with a total collapse of the circulation.

**The Cardiac Mechanism.** The usual average ventricular rate prior to the onset of syncopal seizures was 92 beats per minute and the rhythm was regular. It was not influenced by deep respiratory effort and pressure over either carotid artery did not slow it. During the time that syncopal seizures were recurring frequently, the basic ventricular rate averaged 150 beats per minute independent of the presence of any premature ventricular beats (Fig. A, 1A-B). The main ventricular deflections were supraventricular in form and the *P* wave preceding each was superimposed upon the *T* wave.

For long periods of from several minutes to several hours at a time, the rapid regular basic sinus rhythm would alternate with a bigeminal rhythm. At first this rhythm was occasionally interrupted by premature beats of the ventricles which appeared after every 3d "basic" ventricular complex (Fig. A, 1B-C). These premature beats were opposite in direction to the main ventricular deflections and they were audible at the apical region of the heart and palpable at the wrist.

Soon the bigeminal rhythm would be interrupted by what appeared clinically as irregular "pulse pauses" of from 35 seconds to 1½ minutes in duration (Fig. A, 2B, 3A-B-C-D; Fig. B, 1A).

As these "pulse pauses" were studied with the patient in the electrocardiographic circuit and the heart sounds and pulses were compared with the movements of the galvanometer string, it was observed that they were the result of rapid ventricular oscillations, only the first 2 or 3 of which could be felt at the wrist or heard at the apical region of the heart. If these rapid and recurring ventricular oscillations lasted at least 8 seconds, then the patient shut his eyes momentarily and marked pallor of the face ensued. If the duration of these ventricular oscillations was 20 seconds, but not more than 40 seconds in duration, a typical Stokes-Adams syndrome would follow with loss of consciousness, stertorous breathing, convulsive movements of the body, and incontinence of feces and urine. Spontaneous revival would take place with the first effectual contraction of the ventricles as could be seen from watching the galvanometer string.

The basic ventricular complexes following each alternate premature ventricular beat during the presence of regular bigeminal rhythm were preceded by a distinct *P* wave with a *P-R* interval measuring 0.12 seconds (Fig. A, 2A-B). The addition of any further extra ventricular deflections to this existing bigeminal rhythm completely disrupted this sequence of events so as to produce an irregular and rapid ventricular rate with a pulse deficit simulating very closely the rhythm of auricular fibrillation. At such times the auricular complexes could hardly be discerned in the electrocardiograms

except occasionally, when they would reappear with the reestablishment of the bigeminal rhythm (Fig. A, 2, 3B-C).

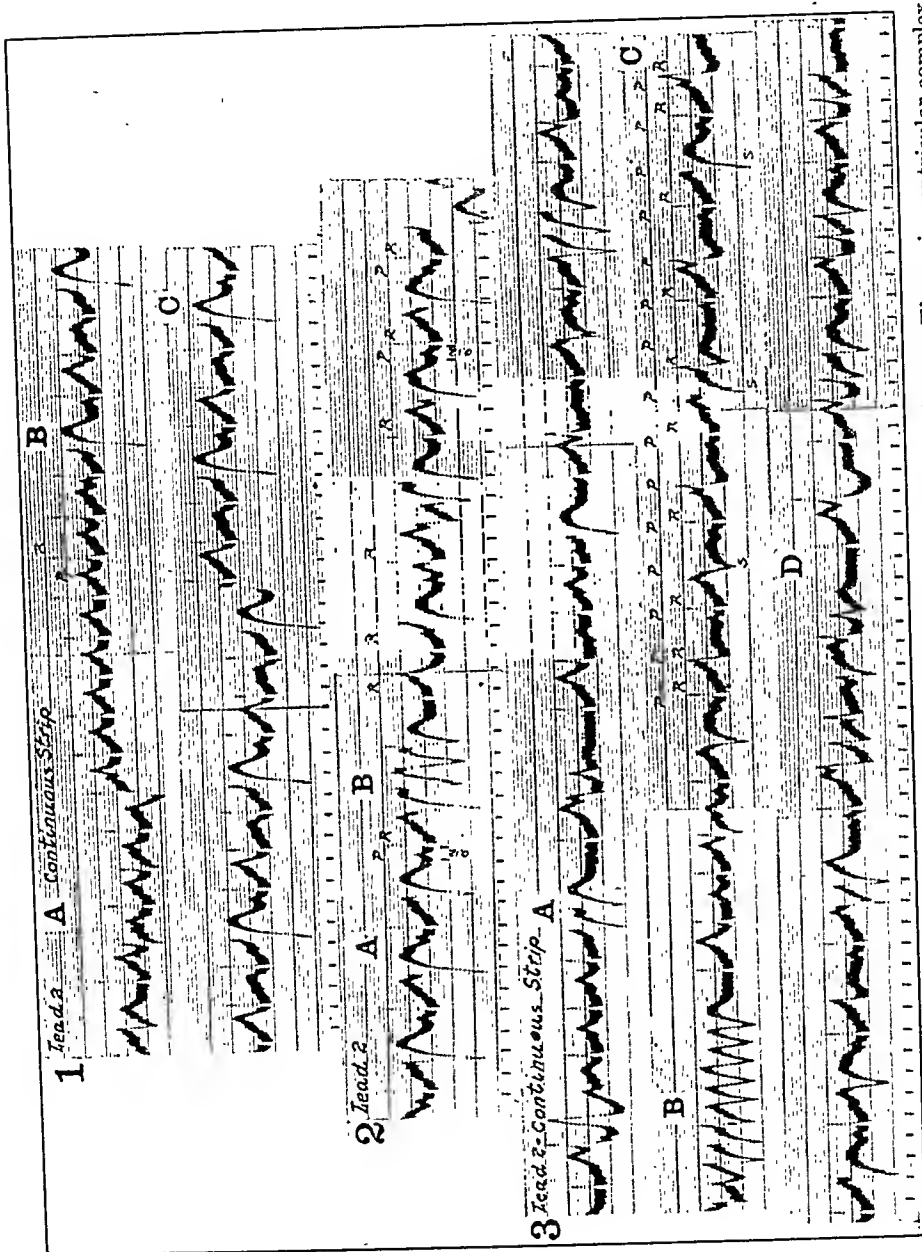


FIG. A.—1A-B, The basic ventricular rate is accelerated to 150 beats per minute. The main ventricular complex is upright and the T wave is superimposed upon the P wave. B-C, A premature ventricular beat appears after every third ventricular complex. It is opposite in direction to the main ventricular deflection. 2A, The basic rhythm is interrupted by alternate premature ventricular beats. B, Recurrent ventricular oscillations, the initial beat of which is similar to the alternate premature ventricular beats. Note the irregular ventricular rate due to the haphazard appearance of multiple premature ventricular beats. 3B, Recurrent ventricular oscillations, only the first two or three of which could be felt at the pulse or heard at the apical region of the heart, resulting in "pulse pauses." B-C, The auricular rate is not disturbed during the presence of alternate premature ventricular beats.

Each of the "pulse pauses" consists electrocardiographically of groups of three or more recurrent ventricular oscillations so superimposed upon each other as to increase their rate to almost 300 per minute. They are characterized by ventricular deflections of variable size in height, each group being ushered in by an "initial"



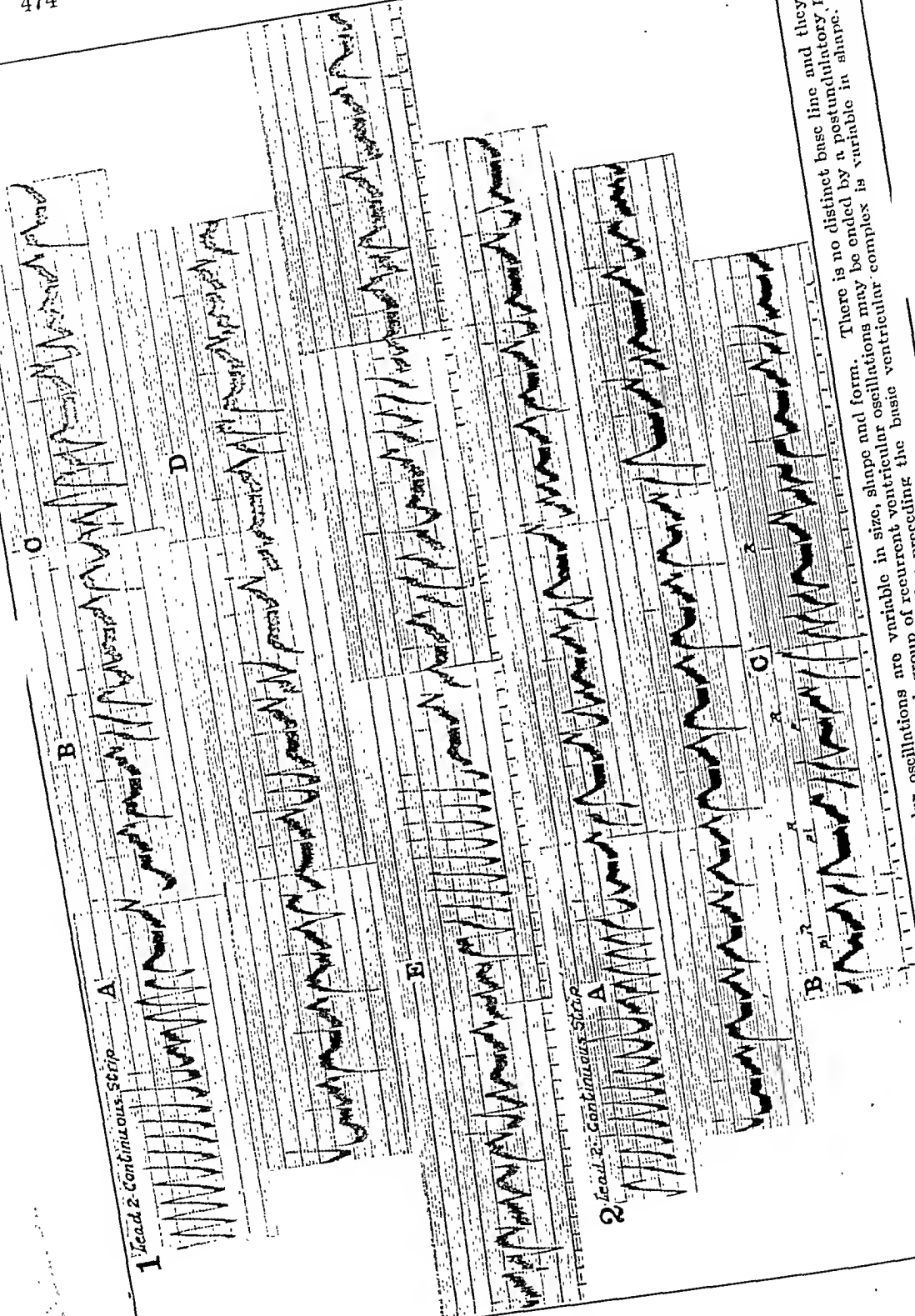


FIG. B.—(A-B-C-D-E, The recurrent ventricular oscillations are variable in size, shape and form. There is no distinct base line and they change abruptly both in voltage and direction from time to time. Each group of recurrent ventricular oscillations may be ended by a postundulatory pause (A and E) or by recurrent extrasystoles (B). 2B-C. Note the auricular complex preceding the basic ventricular complex is variable in shape, size and form depending upon its nearness to the ventricular complex.

ventricular complex which is most often opposite in direction to the main ventricular deflection of the basic rhythm. This "initial" beat preceding each short recurrent group of ventricular oscillations is usually at a definite and equal distance from the preceding basic beat. It follows an upwardly directed *P* wave or occurs simultaneously with it. It is very likely, however, that the presence of this "initial" beat bears no relationship to the preceding auricular complex and that it is an independent extra ventricular contraction which arises spontaneously from the ventricles and is fortuitously placed at this interval from the *P* wave. For if this "initial" beat were the result of an impulse arising in the auricle, it should be of the same shape, size, and form and be always at a certain distance from the *P* wave preceding it. But it has been pointed out that this is not so since some of the "initial" beats are occasionally opposite in direction to the usual forms present, and yet the *P* wave preceding these is at the same interval apart.

The ventricular oscillations which follow this "initial" ventricular beat increase in size from beat to beat. They present no distinct isoelectric line and after several of these beats have occurred, they may change abruptly in direction and in shape, size, and form, being more widely spaced as the mechanism is ended by a post-undulatory pause.

Each of these recurrent short runs of ventricular oscillations ends with a postundulatory pause and is followed immediately by a basic ventricular complex which may or may not be preceded by a definite *P* wave with a well-defined *P-R* interval (Fig. B, 2B-C).

The basic ventricular complexes remain of the same shape and size, whether they follow a *P* wave at a definite *P-R* interval or whether they follow a postundulatory pause, and are not preceded by an auricular beat, indicating that the latter ventricular beats originate probably in the upper part of the auriculoventricular node and are independent of the auricular excitatory process originating in the normal sinus pacemaker.

**Discussion.** These electrocardiograms show that the preliminary disturbances which disrupted the normal cardiac mechanism in this boy prior to the onset of syncopal seizures due to ventricular fibrillation are of a very distinct nature.

They represent essentially a normal sinus rhythm with a rapid rate which is at first interrupted by the occasional interposition of premature ventricular beats of a definite shape or form. These increase in frequency so as to appear alternately at first. There are then added to these premature ventricular beats, in an irregular and unpredictable manner, groups of two or more recurrent and superimposed aberrant ventricular oscillations which, because of their frustrate character, produce "pulse pauses" with corresponding absent heart sounds.

The "pulse pauses" alternate in a haphazard fashion with an

irregular ventricular rate, due partly to impulses originating in the auriculoventricular node and partly to recurrent extraventricular contractions that are frequently followed by normal ventricular complexes. These latter are preceded at regular intervals by an auricular contraction, which apparently arises from the sinus node.

There is thus a definite interplay of two centers within the heart, each sending out impulses at its own rate, the sinus node gaining the ascendancy when a definite *P* wave is seen preceding the basic ventricular complex at an interval of 0.12 second and the auriculoventricular node becoming the pacemaker after the short post-undulatory pauses that follow the interruption of normal rhythm by at least two or more recurrent ventricular oscillations.

These recurrent groups of ventricular oscillations are short runs of ventricular fibrillation. It is their interposition in the electrocardiographic tracings which indicate that any Stokes-Adams seizures that may have developed or will develop in any one patient subsequent to their appearance are due to the persistence or to the perpetuation of their mechanism.

It may be argued and justly so, that since these accompanying records were obtained only a short time prior to death, they represent terminal cardiac irregularities such as have been described by Gallavardin and his associates<sup>4,5</sup> and considered by them as characteristically "pre-fibrillatory" in nature.

These observers have classified as pre-fibrillatory arrhythmias a type of irregularity of the ventricles consisting of salvos of polymorphous extrasystoles, each of which is distinctly separated from the other, some with and others without any compensatory pauses and usually observed only terminally before death. Levy<sup>6</sup> has termed these alterations in rhythm "ventricular anarchy" because of the complex, irregularly alternating and bizarre nature of the ventricular deflections which make up these arrhythmias and which appear shortly before the death of those in whom they are seen.

Such alterations in rhythm have also been observed in the course of auricular fibrillation following overdosage with digitalis bodies.<sup>7</sup> Others have been noted as being more regular in sequence and alternating in character.<sup>8</sup> Still another mechanism consists of shorter and longer runs of a regular ventricular tachycardia with interpolation of polymorphous extrasystoles occasionally interrupting the basically accelerated heart.<sup>9</sup> Finally, even the generally accepted runs of ectopic supraventricular tachycardias, the so-called *Maladie de Bouveret* of the French, have been considered as being the premonitory mechanism of ventricular fibrillation, since such tachycardias have been seen to precede sudden death in many patients in whom they have appeared abruptly.

The criticism of the assumption that any irregular rapid and bizarre action of the heart or regular ectopic ventricular tachycardia is necessarily a "pre-fibrillatory" state of the ventricles is that there

are few records available of the end periods of these alterations in rhythm to prove that ventricular fibrillation has been the terminal phenomenon.

On the contrary, it would appear from recent studies at the Montefiore Hospital that patients dying in the course of a tachycardia of ventricular origin may go into ventricular standstill without any evidence of ventricular fibrillation. Indeed, judging from other evidences obtained of the dying heart,<sup>10</sup> it would appear that ventricular standstill is the rule rather than the exception in the "ultimum moriens" of the heart. Again when short runs of ventricular fibrillation have been observed as terminal phenomena they have been preceded and followed by irregular standstill of the ventricles with a marked slowing of the heart and not an acceleration as was present in this boy.<sup>11</sup>

Furthermore, these short runs of ventricular fibrillation described in this study, which may be appreciated from their pictorial representation much better than from the verbal descriptions, resemble in every respect similar graphic events observed to precede syncopal accidents in other patients in whom electrocardiograms obtained during major syncopal attacks revealed the underlying mechanism to be due to transient ventricular fibrillation. Some of these patients are still living 3 years after the onset of their seizures.

**Summary and Conclusions.** 1. Clinical manifestations were correlated with electrocardiograms of the alterations in the rhythm of the heart of a boy with infectious myelitis during a period when he was experiencing recurrent syncopal attacks, each of several minutes duration.

2. Prior to such seizures there was at first an acceleration of the basic sinus rate from an average of 90 to 150 beats per minute, but the rhythm was regular.

3. Sooner or later, in an unpredictable manner, premature ventricular beats began to disrupt the basic rhythm, first appearing after every fourth normal beat and then alternately after every other normal beat.

4. To these premature beats there were added from time to time recurrent groups of aberrant ventricular oscillations, only the first 2 or 3 of which could be heard at the apical region of the heart or felt at the pulse, thus resulting in periodic irregular "pulse pauses."

5. When the duration of these "pulse pauses" was only 8 or 10 seconds, there was momentary loss of consciousness with pallor of the skin. If they lasted between 20 and 40 seconds there was loss of consciousness. If they were of a duration longer than 40 seconds, there resulted a typical Stokes-Adams seizure with loss of consciousness, epileptiform convulsions, incontinence of feces and urine and stertorous breathing ending in apnea with intense cyanosis.

6. These recurrent periods of aberrant ventricular oscillations are short runs of ventricular fibrillation and their presence in the

electrocardiographic tracings was the most characteristic feature of the alterations in the rhythm of the heart that preceded syncopal seizures in this patient.

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### STUDIES ON TRANSIENT VENTRICULAR FIBRILLATION.

#### II. OBSERVATIONS ON THE ALTERATIONS IN THE RHYTHM OF THE HEART PRECEDING SYNCOPAL SEIZURES IN A WOMAN WITH TRANSIENT AURICULOVENTRICULAR DISSOCIATION.

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FROM previous observations on the alterations in the rhythm of the heart which precede ventricular fibrillation,<sup>1</sup> it was to be expected that not every patient subject to transient seizures of ventricular fibrillation would have this abnormal mechanism ushered in, in exactly the same manner. Nevertheless, while fundamentally the basic rhythm may be different in individuals subject to such seizures, preliminary disturbances heralding transient periods of ventricular fibrillation associated with syncope are somewhat similar.

The following case demonstrates the clinical and graphic manifestations preceding transient ventricular fibrillation in a woman who ordinarily showed partial heart block alternating with normal sinus rhythm.

**Case Report.**—E. E., a female, aged 56 years, was first seen by one of us (L. H.) during the second week of April, 1932. She complained of recurrent attacks of unconsciousness accompanied at times by convulsions, of head-

aches and shortness of breath on climbing stairs. These symptoms were of three months' duration.

In January, 1932, she first began to experience what she described as "short fainting spells." Suddenly and without any warning signs, her usual routine would be interrupted by a feeling of "light headedness," at first lasting only a few seconds at a time but then increasing in duration as the symptoms progressed. Things would get black before her eyes and there were alternating periods of light and darkness lasting as long as a half hour, during which she felt faint, nauseated, and was compelled to sit in one place. Such episodes would come and go in brief paroxysms and on one occasion she fell to the floor, unconscious of her surroundings and had to be helped to bed. Peculiarly enough, when seen by a physician on a day following a prolonged seizure of syncope, her heart rate was 70 beats per minute and the rhythm was noted to be regular. The longer attacks of unconsciousness became more frequent during the month of February, 1932. At first she would have them for a few hours each day and then she would be free from such seizures for several days at a time. Now, these attacks were often accompanied by incontinence of urine and of feces, in addition to what the family described as "convulsions." These seizures must have taken place during her sleep also, for she would be frequently awakened to find her bed linen soiled, although she could not remember anything that took place previously. In between such attacks she would feel perfectly well and be up and about as if nothing had happened to her. During the ensuing 2 months she began to complain of persistent pains in the right upper quadrant in addition to her other symptoms, and in April, 1932, she developed an elevation of temperature accompanied by nausea and vomiting. Because of these complications she was admitted to the private pavilion of Sydenham Hospital for study and observation.

*Physical examination* at that time revealed a well-preserved woman, alert and intelligent, who answered questions rationally. Her right carotid artery was slightly thickened and tortuous. The apical impulse of her heart was in the 6th intercostal space in the anterior axillary line. The heart sounds were of good quality and the first sound was partly replaced by a loud blowing systolic murmur. The aortic second sound was slightly accentuated. The heart rate averaged 75 beats per minute and the rhythm was regular. The blood pressure was 229 systolic and 120 diastolic. A few moist râles could be heard over the bases of the lungs posteriorly. The abdomen showed slight rigidity in the right upper quadrant. The edge of the liver was not felt. There was a round mass about the size of a small orange palpable about 4 cm. below the right costal margin in the mid-clavicular line. It was extremely tender. The lower extremities showed no edema.

Because of the persistent signs in the abdomen, the patient was operated upon for cholecystitis during the third week of April, 1932. She withstood the operation successfully and remained free from syncopal attacks for the ensuing 2 months, when their reappearance compelled her to enter the Beth Israel Hospital on June 16, 1932. She remained at that institution for almost 1 month when her Stokes-Adams seizures became less frequent and finally disappeared entirely before she was discharged.

On January 18, 1933, she began to experience recurrent syncopal attacks lasting several minutes at a time. On the following day she died following one of these long seizures.

**Cardiac Mechanism.** While she was under observation, repeated electrocardiograms were taken. These were correlated with her clinical manifestations and they showed an unusual and unique sequence of events. Her basic rhythm alternated for long periods

at a time between that of a normal sinus rhythm and auriculo-ventricular dissociation. The normal sinus rhythm was characterized graphically (most of these studies were carried out with Lead II only and unless otherwise specified, comparisons are made of complexes in this lead only) by an upright auricular complex with a *P-R* interval measuring 0.16 second and a notched ventricular complex 6 mm. in height and 0.16 second in width (Fig. A-1). At such times the auricular and ventricular rates averaged 100 beats per minute. Sooner or later the basic ventricular rate of the sinus rhythm was halved (Fig. A-2). It will be observed that this halving was due to what appears to be blocked auricular beats. However, the *P-R* interval following a blocked auricular beat (Fig. A-2-2B) is shorter than the one preceding the basic ventricular complex (Fig. A-2A) and the main ventricular deflection following the shortened *P-R* interval is different in size, shape, and form from the usual complexes.

For hours at a time the auricular as well as the ventricular rates, in the presence of auriculoventricular dissociation, were unusually labile. At times the auricles beat at the rate of 120 beats per minute and a bigeminal rhythm resulted (Fig. A-3), when the electrocardiograms revealed an apparent 3:2 block, 3 auricular contractions being present to every 2 ventricular contractions. A slowing of the ventricular rate to 54 beats per minute was accompanied by an auricular rate of 100 beats (Fig. A-4).

Suddenly the ventricles would slow to 46 beats (Fig. A-5) and the auricles to 89 before they would accelerate again to 100 or 120 beats (Fig. A-6, 7) and the ventricles to 54 or 60 beats. At such intervals the shape of the *T* waves would be altered by the superimposed auricular deflections although the main ventricular deflections would hardly be altered.

Frequently, a 3:2 block would occur with a regular auricular rate of 90 and the ventricles beating at 46 per minute (Fig. A-9) before a further slowing of both the auricles and the ventricles would be interrupted by extrasystoles (Fig. B-1A) of a peculiar type, preceded by a shortened *P-R* interval.

At first these single extrasystolic contractions, which increased the rate of the heart beats during the presence of auriculoventricular dissociation, could all be heard over the apical region of the heart and could be felt at the pulse. The bigeminal rhythm could not, however, be distinguished from that produced by the alternate presence of 3 auricular contractions described above (Fig. A-3).

The ventricular complex of the first beat of the bigeminy, due to alternate premature ventricular contractions, was usually similar to the ventricular complex present when there were blocked auricular beats (cp. Fig. B-4A and 4B with Fig. A-2A and 2B). At other times it differed and resembled the basic ventricular complex observed during sinus rhythm.

Occasionally this bigeminal rhythm consisted of an allorhythmia in which a normal sinus beat followed by a premature ventricular contraction (Fig. *E-2A*) appeared periodically after each eighth ventricular contraction (Fig. *E-2A, B, C*). Each bigeminal group consisting of a normal sinus beat and an extra systole was followed

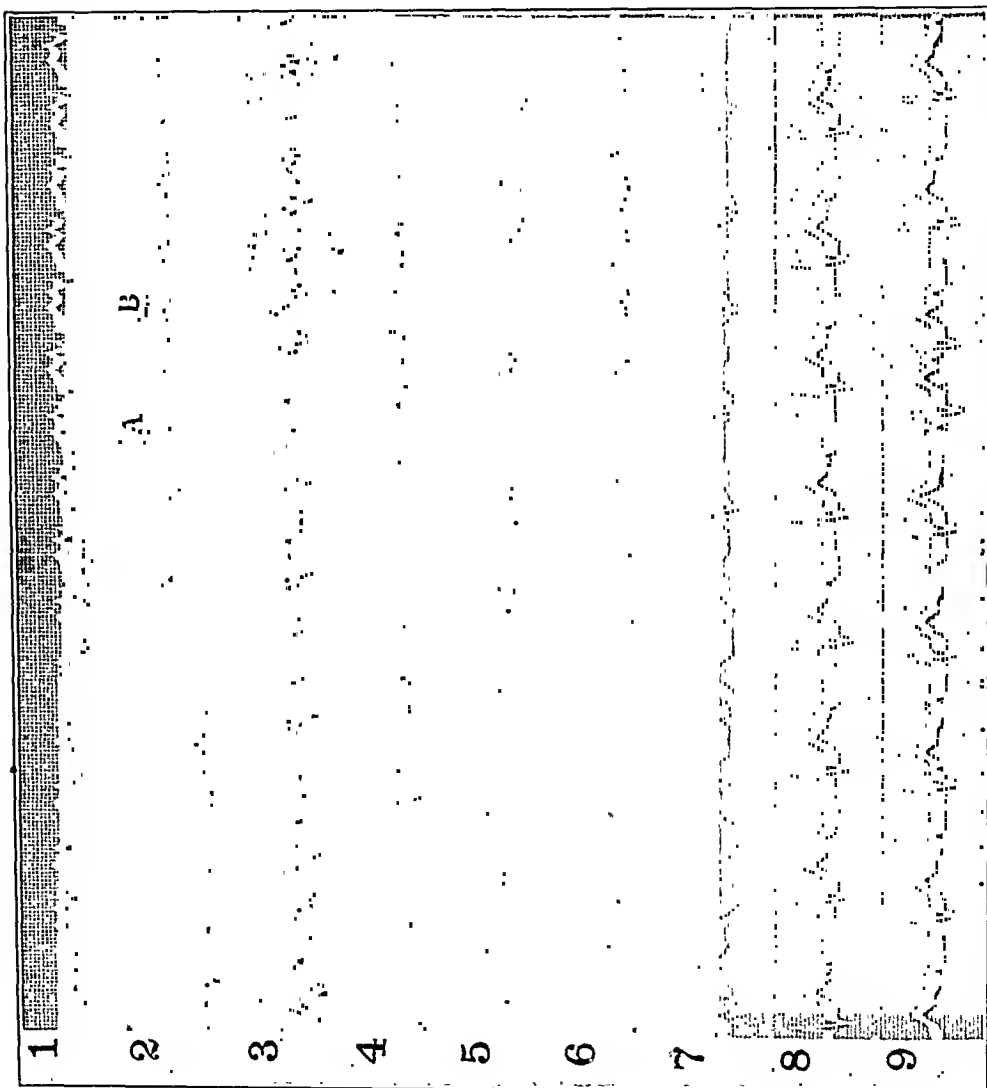


FIG. 4.—(1) The basic sinus rate is 100 beats per minute. (2) Both the *P* and *Q-R-S* complexes of the basic sinus rhythm are different from those present during transient auriculoventricular dissociation. (3) 3 to 2 block (4, 5, 6, 7, 8, 9). The rate of the auricles as well as that of the ventricles waxes and wanes during established auriculoventricular dissociation.

by a series of bigeminal beats in which the first complex was idioventricular, without any definite auricular wave or *P-R* interval preceding it and it was totally different in size, shape, and form from the basic ventricular complex.

This would indicate that the heart was under the control of two different centers acting independently of each other, each one send-



ing out impulses of its own, one impulse originating in the sinus node and the other in the auriculoventricular node or in the tissues adjacent to it.

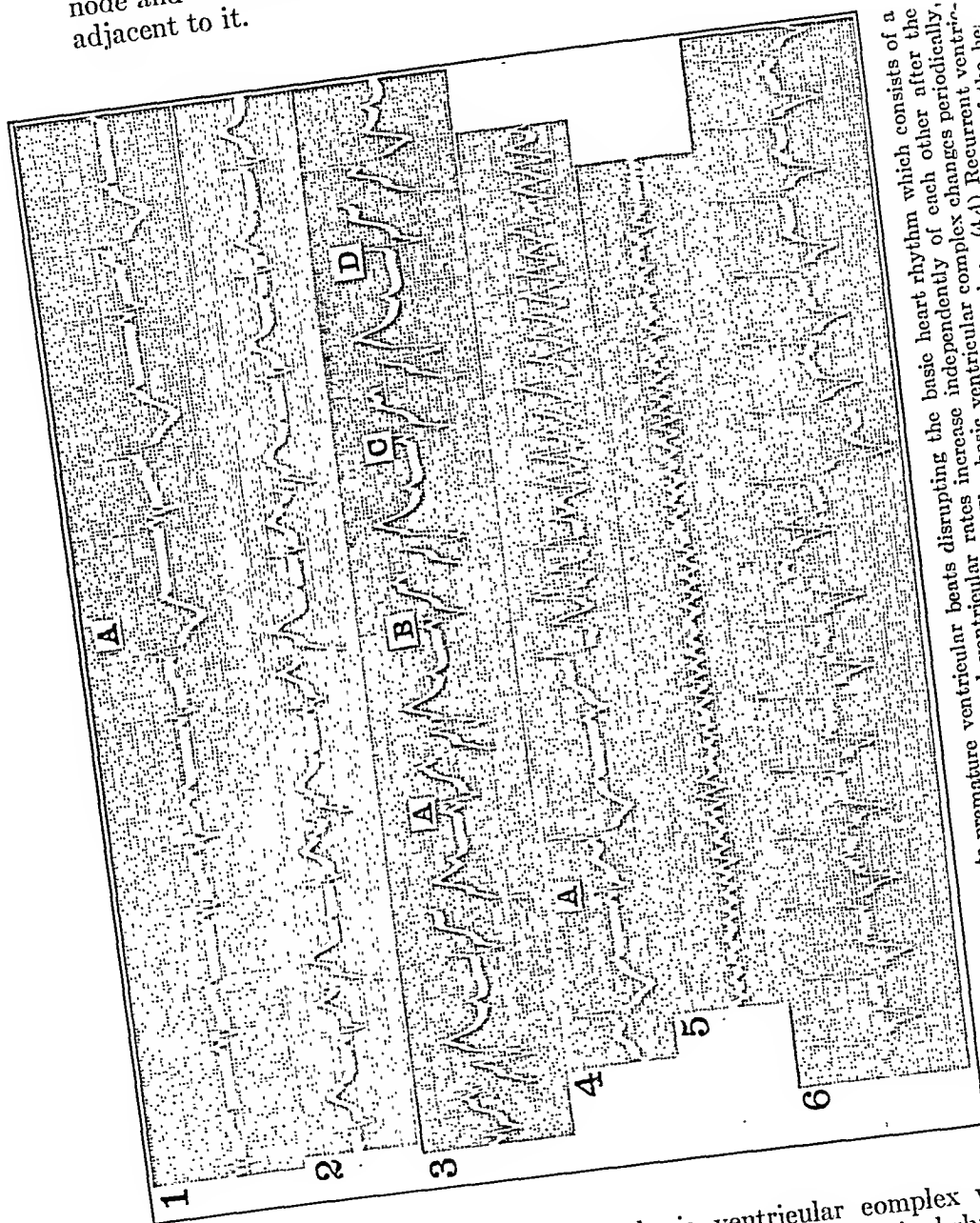


FIG. B.—(1A) Alternate premature ventricular beats disrupting the basic heart rhythm which consists of a 2 to 1 heart block. (2) The auricular and ventricular rates increase independently of each other after the appearance of premature ventricular beats. (3A, B, C, D) The basic ventricular complex changes periodically, this change depending in part upon its distance from the preceding auricular complex. (4A) Recurrent ventricular oscillations associated with ineffectual ventricular contractions may appear when the rhythm of the heart is slow. (5) Record obtained during Adams seizure. (6) The postictal period.

Sometimes the shape of the basic ventricular complex would change from beat to beat especially when, to the bigeminal rhythm, there would be added from time to time, one or more recurrent ventricular oscillations. These ventricular oscillations which ap-

peared in an unpredictable manner, were aberrant in form and only the first two or three could be heard at the apical region of the heart or felt at the pulse. The shape of the basic ventricular complex was dependent at such times upon the distance of the preceding

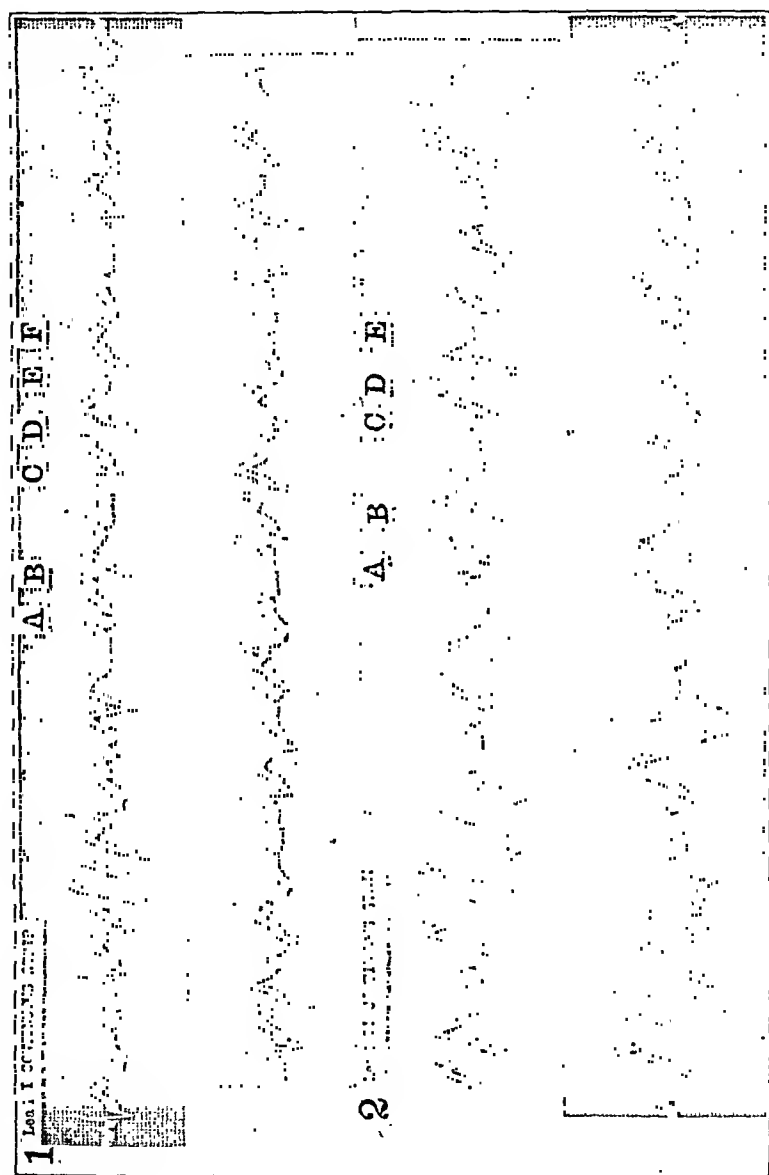


Fig. C.—1C, D, E, F; 2C, D, E, F) A quadrigeminal rhythm interrupting the basic rhythm. A nodal beat (C) is followed by a premature ventricular beat (D). Then a normal beat (E) is also followed by a premature ventricular beat.

P wave from it (Fig. B-3A, B, C, D). As the P-R interval became shorter and shorter, the ventricular complexes became larger and more aberrant. The likelihood of a shift of the pacemaker of the heart from the sinus node to the auriculoventricular node offers the most logical explanation for this phenomenon. This change in

the basic ventricular complex, however, did not alter the shape or rhythm of the additional recurrent ventricular oscillations that would follow it.

As the recurrent ventricular oscillations following a basic ventricular complex increased in frequency, the fundamental mechan-

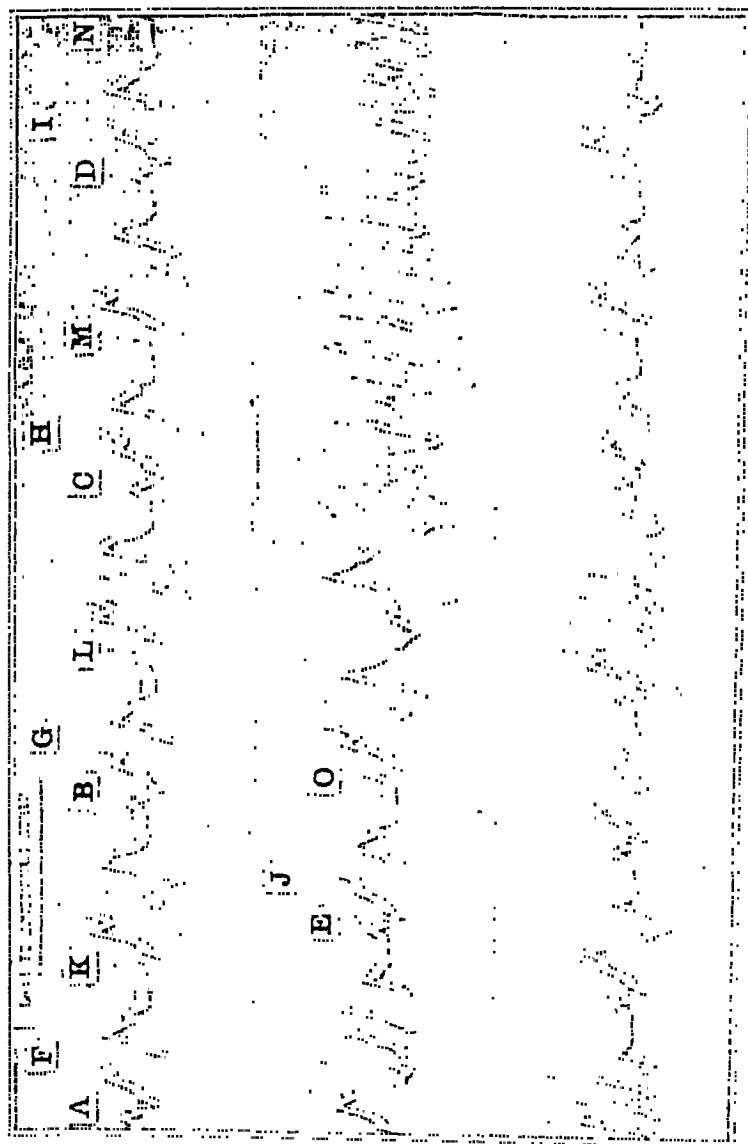


FIG. D.—An allorhythmia consisting of a normal beat (A, B, C, D, E), a premature beat (F, G, H, I, J), and a nodal beat (K, L, M, N, O) precedes a short run of ventricular fibrillation (O).

ism of the heart assumed a quadrigeminal rhythm which lasted for minutes or sometimes hours at a time (Fig. C-1C, D, E, F; 2C, D, E, F). This rhythm could be appreciated clinically. The four beats making up this quadrigeminy consisted of a nodal ventricular complex (Fig. C-1C, 2C) preceded by a very shortened P-R

interval and a positive auricular complex, part of which was buried in it. This was followed by a premature ventricular contraction (Fig. C-1 D, 2 D) which in turn was succeeded by a normal basic

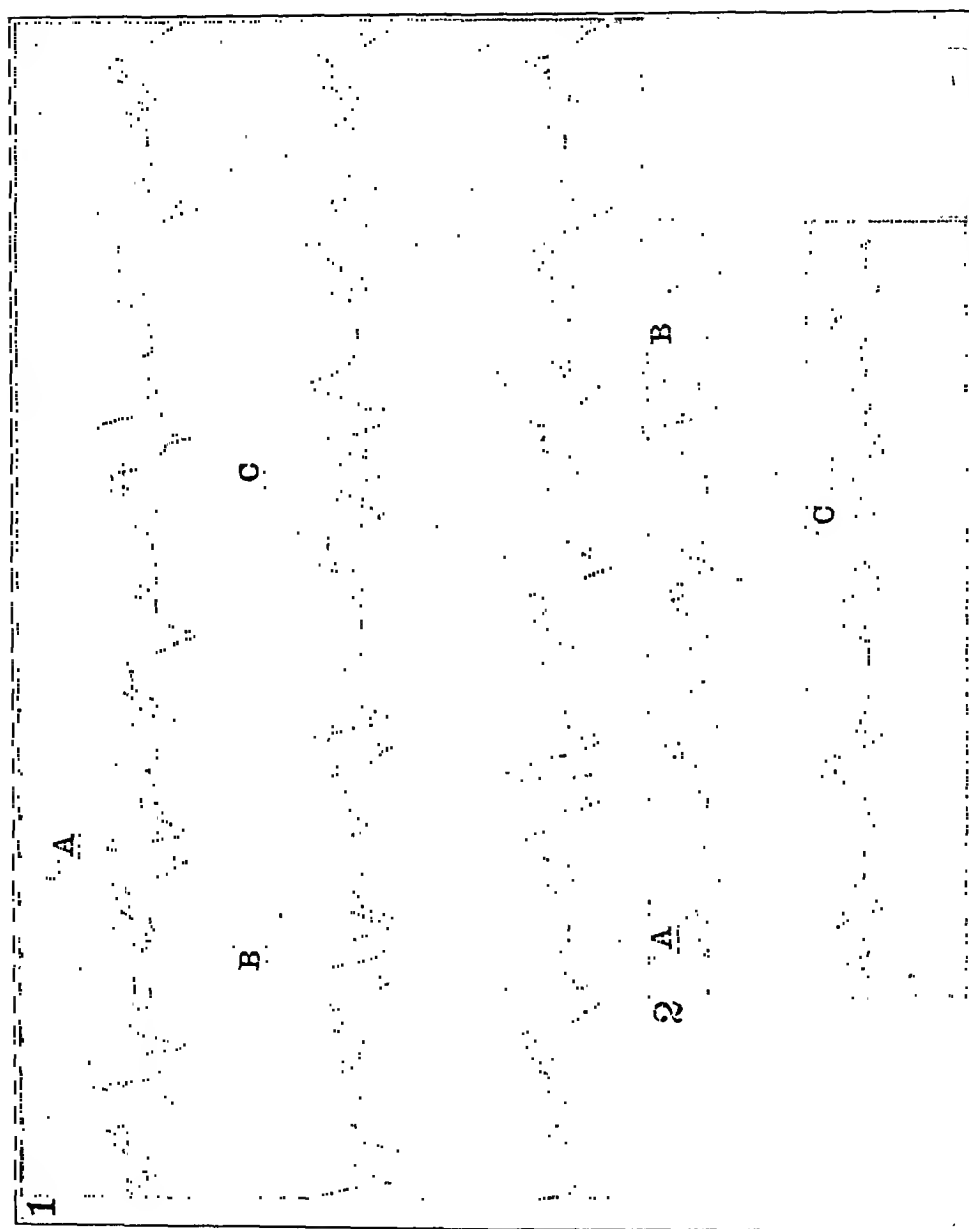


FIG. E.—(1A, B) Recurrent ventricular oscillations may appear after a normal sinus beat or after an idioventricular beat (C). (2A, B, C) A normal sinus beat appears as the 8th ventricular contraction. This rhythm preceded all other allorhythmias encountered in this patient prior to syncopal seizures.

ventricular complex that followed an upright auricular wave with a P-R interval of 0.16 second, similar to that observed during normal sinus rhythm. This normal beat was followed by another premature ventricular contraction, which made up the last element of the

quadrigeminy. The four grouped beats were separated from other similar ones by an interval measuring almost 0.8 second (cp. Fig. C, 1 and 2).

In the mean time, as these allorhythmias were appearing and alternating with other variations in the rhythm of the heart, the patient's clinical condition was not affected. She was conscious of an occasional precordial thump but aside from that, the circulation was adequately maintained. It was not until these abnormal alterations in the rhythm were further disrupted by the addition of recurrent ventricular oscillations appearing in groups of three or more, that the patient began to complain. These additional recurrent ventricular oscillations could be appreciated clinically by the appearance of "pulse pauses" which resulted from the absence of effectual ventricular contractions, since they were frustrane in character and too weak to open the aortic orifice.

It was impossible to predict in any way the appearance and duration of these "pulse pauses." Sometimes they were ushered in when the basic rhythm of the heart was slower (Fig. E-1A, B, C), while at other times when it had been accelerated by the addition of multiple premature ventricular beats (Fig. C-1). At no time, however, in the hundreds of records obtained of these alterations in rhythm preceding a major syncopal seizure were any runs of these ventricular oscillations initiated abruptly without the presence of some of the preliminary events described above.

More often, before a major syncopal attack, the cardiac mechanism consisted of an allorhythmia in which the basic ventricular deflection (Fig. D-A, B, C, D, E) was preceded by a normally shaped auricular complex with a P-R interval measuring 0.16 second. This was followed at an interval of 0.36 second by a premature ventricular beat (Fig. D-F, G, H, I, J). This bigeminal rhythm, with almost constant regularity, was in turn followed by two aberrant ventricular complexes (Fig. D-K) and sometimes by many more (Fig. D-N). (Cp. this mechanism with that of Fig. C.)

The "initial" ventricular complex ushering in the recurrent ventricular oscillations was usually opposite in direction to its preceding beat. It followed a basically normal ventricular complex or a nodal or idioventricular beat. This "initial" beat was most often of the same size and shape and form but its succeeding complexes were extremely variable. They were aberrant, bizarre, changed from beat to beat at times, and showed no definite base line. Frequently, they changed abruptly in duration and direction and would or would not be ended by a postundulatory pause. The auricular beats could not be made out during their presence, although the rate and sequence of the auricular beats was not disturbed.

The clinical manifestations associated with these recurrent ventricular oscillations depended upon their duration at any one time and resembled in every respect the signs and symptoms observed in other patients in whom their persistence for over 40 seconds

resulted in a typical Stokes-Adams seizure with unconsciousness, epileptiform convulsions, stertorous breathing ending in apnea, and intense cyanosis which disappeared with the first effectual contractions that initiated spontaneous revival of the heart.

The period following immediate revival of the heart consisted of an intermediary idioventricular rhythm with a rapid irregular idioventricular rate that slowed after several minutes to either the sinus rhythm or the allorhythmia which preceded the onset of syncope during established auriculoventricular dissociation.

**Discussion.** The accompanying electrocardiograms reveal the successive alterations in the rhythm of the heart preceding syncopal seizures in this woman to have consisted at first of the development of transient auriculoventricular dissociation, so that a normal heart rate of 100 beats per minute was slowed to one-half its original. The transition from a normal rhythm to a halved one was not abrupt but gradual and there were alternating periods of normal sinus rhythm with dissociation for some time before dissociation persisted. There was a marked waxing and waning of both the auricular and ventricular rates during the presence of established dissociation of the auricles from the ventricles. An acceleration or retardation of the auricles did not influence, however, the ventricular rate or *vice versa*.

It is not within the province of this study to give a detailed explanation of the mechanism responsible for the various allorhythmias encountered in this patient. It will suffice to state that the occasional recurring and periodic presence of a normal sinus beat during established auriculoventricular dissociation indicates that the heart during such periods was activated by two centers, each sending out impulses of its own, one superceding the other by virtue of changes in the refractoriness of the auriculoventricular node and bundles resulting in a so-called para-arrhythmia<sup>2</sup> with interference and dissociation.<sup>3</sup>

All of these variations in the rhythm of the heart yielded an acceleration of the ventricular rate during block and it is very likely that this increase in the ventricular rate is a very necessary precursory mechanism in the development of the subsequent changes that precede ventricular fibrillation. For an increase in the ventricular rate above that of the usual basic rate has already been observed in other patients with similar symptoms and signs. (Preceding article.)

Of greater importance, in addition to the increase in the ventricular rate, is the fact that a major syncopal seizure was invariably heralded by the appearance of short runs of ventricular oscillations, which in their final analysis turn out to be short runs of ventricular fibrillation.<sup>4</sup> It is their presence in the electrocardiograms which predicates longer runs of a similar nature that finally result in syncope. Since no other types of syncopal seizures have been observed to be preceded by similar events in the cardiac mechanism, it is fair to assume that these recurrent groups of ventricular oscilla-

tions are pathognomonic for syncope associated with ventricular fibrillation.

**Summary and Conclusions.** 1. Successive electrocardiograms were correlated with the clinical manifestations of a woman who was suffering from recurrent syncopal seizures. Particular attention was paid to the alterations in the rhythm of the heart that preceded syncope.

2. The patient usually showed normal sinus rhythm in between attacks. For some time prior to a seizure, the normal sinus rhythm alternated with that of auriculoventricular dissociation.

3. There was a marked waxing and waning of the rates of both the auricles and ventricles during the presence of auriculoventricular dissociation.

4. Sooner or later this dissociated rhythm would be interrupted by premature ventricular beats coming on singly so as to form a bigeminal rhythm. Occasionally a normal sinus beat would be interpolated in this dissociated rhythm, appearing at first after every 8th effectual ventricular contraction and then more frequently. Alterations between the normal sinus rhythm and the dissociated rhythm resulted in grouped beats forming trigeminies and quadrigeminies with regular periodicity.

5. When the appearance of these various rhythms had materially increased the rate of the ventricles after they had been slowed during auriculoventricular dissociation, recurrent ventricular oscillations began further to disrupt the cardiac mechanism.

6. These aberrant ventricular oscillations were variable in shape, size, and form from beat to beat. They were associated clinically with ineffectual ventricular contractions resulting in periodic "pulse pauses," absent heart sounds, and a collapse of the circulation.

7. If these ventricular oscillations lasted from 8 to 10 seconds, then the patient merely shut her eyes and her face assumed an ashen gray pallor. If they were of 20 seconds, duration she lost consciousness. If they lasted longer than 40 seconds a typical Stokes-Adams seizure ensued.

8. These short groups of ventricular oscillations are short runs of ventricular fibrillation and no syncopal seizure resulting from ventricular fibrillation appeared without these shorter runs heralding a major attack. Because of this, they are pathognomonic for ventricular fibrillation and their recurrent presence in any electrocardiogram should help in the diagnosis of the cardiac mechanism underlying such syncopal seizures.

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## CLINICAL EVALUATION OF LEAD IV (CHEST LEADS).

### A SURVEY OF LEAD IV IN AMBULATORY CASES OF CORONARY ARTERY DISEASE AND ACUTE CORONARY OCCLUSION.

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ANY clinical method that promises a possibility of arriving at more exact diagnosis deserves attention. This is especially true if the method is not cumbersome and can be used in both office practice and at the bedside.

In 1932, Wolferth and Wood<sup>1</sup> published the results of a study of Lead IV as an electrocardiographic aid in the diagnosis of coronary occlusion. A number of authors since that time have reported their findings with this method, namely, Lieberman and Liberson,<sup>2</sup> Katz and Kissin,<sup>3</sup> and Hoffman and Delong.<sup>4</sup> To date, however, the cases reported have been mainly hospital cases, presenting definite clinical evidence of coronary artery disease, with or without occlusion.

The series reported herein have been chosen from private practice. All the 86 patients were ambulatory except 13, who were studied with the aid of a portable electrocardiograph, first at home during an acute attack and later in the office. Forty of the 86 patients had definite clinical symptoms of coronary artery disease, with or without a history of acute occlusion. Some of these 40 had a symptom complex of angina pectoris. In addition 8 non-coronary cardiac cases and 25 non-cardiac cases for control were studied.

The purpose of the study was to see whether Lead IV would be positive only in those cases where the routine 3 leads were positive, or whether it might sometimes be positive while the routine 3 leads were negative. If the 4th lead were positive only in conjunction with positive routine 3 leads, it would be superfluous as an additional method; but if it should prove positive in any case where the routine 3 leads were negative or doubtful, it would be of definite value.

**The Method.** The method of Wolferth and Wood was carried out, after employing the method customarily used for the routine 3 leads. The cardiac region anteriorly and the spinal region medial to the right scapula posteriorly were thoroughly scrubbed with warm saline water to make these areas hyperemic. The electrodes were held firmly in place over the corresponding areas by bandaging the patient's chest tightly. The lead wire of the right arm was connected to the plate anteriorly, while that of the left arm was connected posteriorly. Those cases in whom the arm leads were reversed, as mentioned by Wolferth and Wood, and carried out by Lieberman and Liberson, are designated in our series by the letter B. We did not find it necessary to shave the skin or hold the plates by a special paste as advocated by Katz and Kissin, or to utilize special electrodes as suggested by Hoffman and Delong.



**Normal Lead IV.** Fig. 1 shows the variation of complexes found in the 25 normal control cases. Most of the complexes show a negative *P* wave. The *Q-R-S* complexes are diphasic, with a definite deep *Q* wave and inverted *T* wave. The *T* waves are inverted in most cases and diphasic in only 2 (Cases 323 and 332). The depth of the *T* wave varies from 2 to 9 mm., the average depth being 4.9 mm. (Table 1).<sup>\*</sup> The *Q-R-S* complexes are not slurred and are slightly higher than in the routine 3 leads. By reversing the arm leads, as in Case 508*B*, a reverse image of the above complexes is seen. In the reverse position, the *T* waves are upright and there is an *S* wave in place of the deep *Q* wave. When interpreting Lead IV electrocardiograms, one must be careful to remember the method employed, an inverted *T* wave being normal in the anteroposterior position.

TABLE 1.—AVERAGE DURATION AND HEIGHT OF COMPLEXES IN NORMAL LEAD IV.

Case No.	Height of <i>P</i> waves, mm.	<i>P-R</i> interval, sec.	<i>Q</i> complex, mm.	<i>Q-R-S</i> complexes.		<i>T</i> waves, mm.
				Height, mm.	Width, sec.	
323 . . .	-1	0.16	-3	+9	0.08	-2
332 . . .	-1	0.12	-5	+18	0.08	-3
351 . . .	-1	0.16	-10	+12	0.08	-8
361 . . .	+1	0.12	-10	+15	0.08	-4
417 . . .	+1	0.12	-6	+18	0.08	-6
428 . . .	0	0.12	-7	+12	0.08	-7
429 . . .	-1	0.16	-7	+13	0.04	-6
430 . . .	-1	0.16	-5	+15	0.08	-6
432 . . .	-1	0.16	-4	+15	0.04	-6
440 . . .	-1	0.16	-5	+14	0.08	-5
441 . . .	-1	0.12	-6	+13	0.08	-4
447 . . .	-1	0.12	-4	+11	0.08	-3
450 . . .	-1	0.12	-5	+12	0.08	-6
473 . . .	+1	0.12	-7	+11	0.08	-4
475 . . .	-1	0.12	-8	+9	0.04	-4
476 . . .	-1	0.16	-14	+13	0.08	-6
478 . . .	-1	0.12	-10	+7	0.12	-8
482 . . .	-1	0.12	-10	+7	0.08	-3
483 . . .	-1	0.12	-9	+9	0.12	-7
493 . . .	-1	0.16	-9	+9	0.08	-5
495 . . .	-1	0.16	-6	+6	0.04	-2
497 . . .	-2	0.12	-5	+10	0.08	-3
498 . . .	-2	0.12	-8	+9	0.12	-5
506 . . .	+1	0.12	-10	+10	0.08	-5
507 . . .	-1	0.12	-7	+9	0.04	-5
Average . .	-0.6	0.134	-7.2	+10.8	0.076	-4.9

**Lead IV in Coronary Artery Disease With Myocardial Damage.** Forty of our cases came to the office complaining of what they thought was a gastro-intestinal disturbance. Inquiry revealed that the symptoms were most probably due to coronary artery disease; in several cases, there was actually a definite history of an acute

<sup>\*</sup> Acknowledgement is hereby gratefully given Mr. Paul K. Roht for his assistance in preparing the tables.

Patient 332.

Patient 508.

*a*

*b*

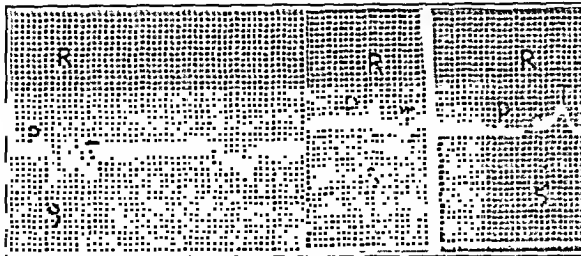


FIG. 1.—Types of normal Lead IV. *a*, Anteroposterior position; *b*, posteroanterior position.

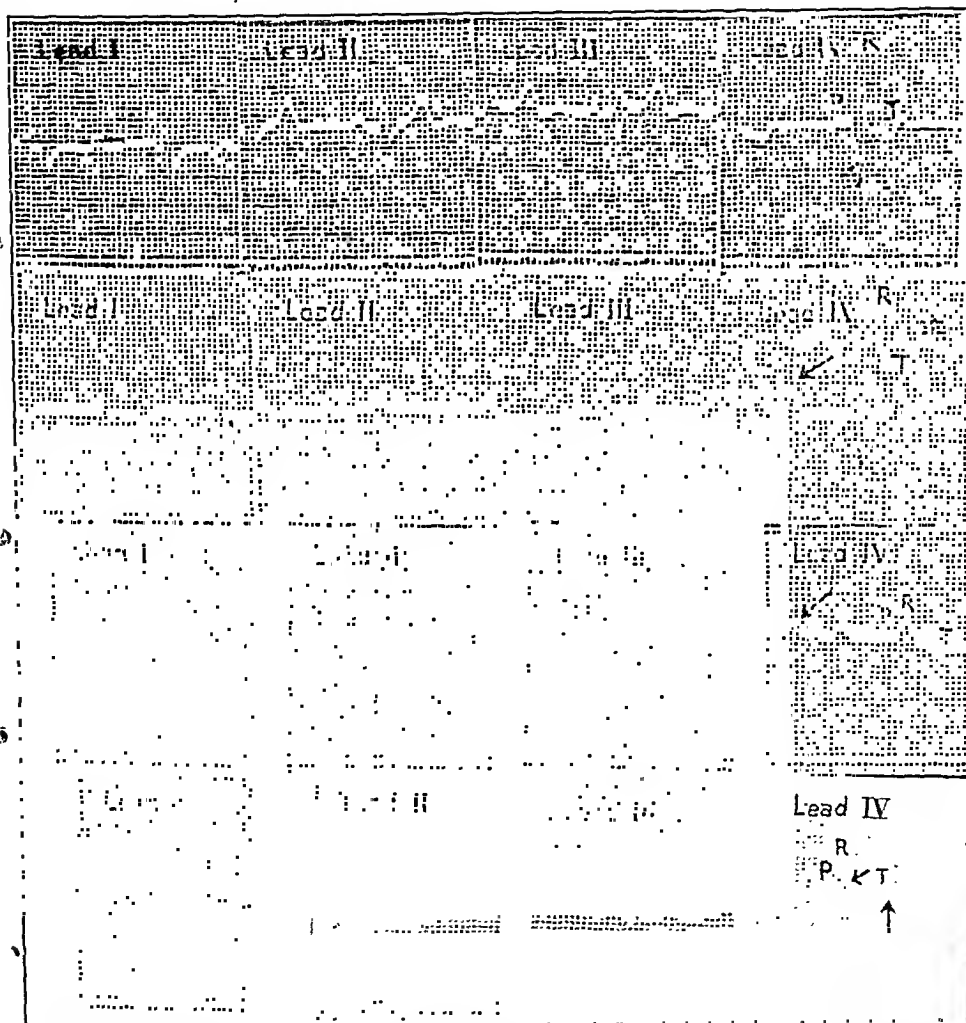


FIG. 2.—Cases of coronary artery disease, showing the routine three leads with variant types of Lead IV (normal and abnormal).

TABLE 2.—AVERAGE DURATION AND HEIGHT OF COMPLEXES IN LEAD IV OF CORONARY ARTERY DISEASE. COMPARATIVE EVALUATION OF THE ROUTINE THREE LEADS AND LEAD IV.

Case No.	Height of P waves, mm.	P-R interval, sec.	Q complex, mm.	Q-R-S complex		T waves, mm.	Blood-pressure, mm.	Lead I.	Lead II.	Lead III.	History.	Evaluation of routine leads.	Lead IV.
				Height, mm.	Width, sec.								
324	-1	0.16	-7	+15	0.08	-2	140/80	Diphasic T <sub>1</sub>	.....	T <sub>2</sub> above line	+	+	-
349	-1	0.12	-6	+17	0.08	-2	96/60	T <sub>1</sub> above line, slurring	T <sub>2</sub> above, slurring	Low, slurring	+	+	+ slurring.
352	-1	0.12	-7	+16	0.08	+2	90/60	Slurring	Slurring	Q <sub>2</sub> deep, slurring	+	+	-
355	-1	0.12	-9	+7	0.08	-5	130/80	.....	T <sub>2</sub> diphasic	Inverted	+	+	-
372	0	0.16	-10	+7	0.08	-5	90/60	.....	T <sub>2</sub> upright	T <sub>2</sub> inverted	+	+	-
376	-1	0.16	-9	+9	0.08	-3	160/90	.....	Slurring	Slurring	+	+	-
402	+1	0.16	-7	+15	0.01	-3	130/80	Slurring	Slurring	T <sub>2</sub> above line	+	+	+
407	+1	0.16	-1	+4	0.08	0	160/90	T <sub>1</sub> inverted	Slurring	.....	+	+	-
418	-1	0.16	-15	+15	0.08	-5	160/90	.....	Slurring	Q <sub>2</sub> deep	+	+	-
420	-1	0.12	-9	+15	0.08	-2	120/90	T <sub>1</sub> inverted, slurring	Slurring	T <sub>2</sub> above line, slurring	+	+	-
421	0	0.12	-4	+15	0.08	+1	140/80	.....	Slurring	Q <sub>2</sub> deep	+	+	-
423	-1	0.12	-9	+15	0.08	-2	135/70	Slurring	T <sub>2</sub> down	T <sub>2</sub> above line, slurring	+	+	-
424	+1	0.16	-2	+15	0.01	+2	80/60	.....	T <sub>2</sub> diphasic, slurring	Q <sub>2</sub> deep	+	+	+ slurring.
426	-1	0.12	-3	+15	0.08	-2	110/70	.....	.....	.....	+	+	-
433	+1	0.12	-3	+10	0.08	-2	100/70	.....	.....	Q <sub>2</sub> deep	+	+	+ slurring.
434	-1	0.16	-10	+13	0.08	-1	100/70	.....	.....	Q <sub>2</sub> deep	+	+	-
436	-1	0.12	-8	+10	0.08	-3	110/70	.....	.....	Q <sub>2</sub> deep	+	+	-
438	-1	0.16	-7	+12	0.01	-3	100/60	.....	.....	Q <sub>2</sub> deep	+	+	-
443	-1	0.12	-5	+11	0.08	-6	130/80	.....	.....	Q <sub>2</sub> deep	+	+	-
448	-1	0.16	-10	+11	0.08	-3	160/80	.....	.....	Q <sub>2</sub> deep	+	+	-
451	-1	0.16	-5	+12	0.08	-4	130/80	.....	.....	Q <sub>2</sub> deep	+	+	-
454	-1	0.12	-7	+9	0.08	-6	110/80	Slurring	Slurring	Slurring	+	+	-
471	+1	0.12	-7	+9	0.08	-6	120/80	T <sub>1</sub> slurring, upright	T <sub>2</sub> diphasic, slurring	T <sub>2</sub> inverted, slurring	+	+	-
483	-1	0.12	-10	+12	0.04	-3	180/90	T <sub>1</sub> diphasic	T <sub>2</sub> diphasic	T <sub>2</sub> diphasic	+	+	-
489	-1	0.12	-10	+12	0.08	-6	140/80	.....	.....	Q <sub>2</sub> deep	+	+	-
467	-1	0.12	-9	+14	0.08	+3	115/90	T <sub>1</sub> inverted	T <sub>2</sub> above line	T <sub>2</sub> above line	+	+	-
468	+1	0.12	-10	+10	0.08	-7	120/80	.....	.....	Q <sub>2</sub> deep	+	+	-
470	+1	0.12	-9	+19	0.01	-3	135/90	.....	.....	Q <sub>2</sub> deep	+	+	-
474	-1	0.16	-10	+7	0.08	-2	130/80	Slurring	Slurring	Q <sub>2</sub> deep, slurring	+	+	-
480	0	0.10	-5	+7	0.08	-7	130/80	.....	.....	T <sub>2</sub> above, slurring	+	+	-
484	-1	0.16	-9	+10	0.08	-2	110/80	.....	.....	Q <sub>2</sub> deep	+	+	-
488	+1	0.12	-9	+12	0.08	-7	90/60	T <sub>1</sub> diphasic	.....	T <sub>2</sub> above	+	+	-
490	-1	0.12	-9	+15	0.08	-9	160/90	T <sub>1</sub> above line	.....	T <sub>2</sub> below	+	+	-
491	+1	0.12	0	+4	0.08	-2	120/60	T <sub>1</sub> inverted, slurring	T <sub>2</sub> diphasic, slurring	T <sub>2</sub> below	+	+	-
492	+1	0.12	0	+8	0.08	-1	110/70	.....	.....	T <sub>2</sub> poor	+	+	-
494	0	0.12	-3	+10	0.08	-2	90/50	T <sub>1</sub> above line	.....	T <sub>2</sub> diphasic	+	+	-
496	-1	0.16	-9	+10	0.01	-7	130/80	Small complexes	Small complexes	Small complexes	+	+	-
500	-1	0.16	-9	+10	0.08	-9	160/60	.....	.....	.....	+	+	-
509	-1	0.12	-9	+8	0.08	-5	140/90	T <sub>1</sub> diphasic	.....	.....	+	+	-
510	-1	0.12	-8	+8	0.08	-3	160/90	.....	.....	.....	+	+	-
Av.	-0.5	0.13	-7.3	+11	0.07	-3.4							

coronary occlusion which had been erroneously interpreted by the patient as an attack of acute indigestion.

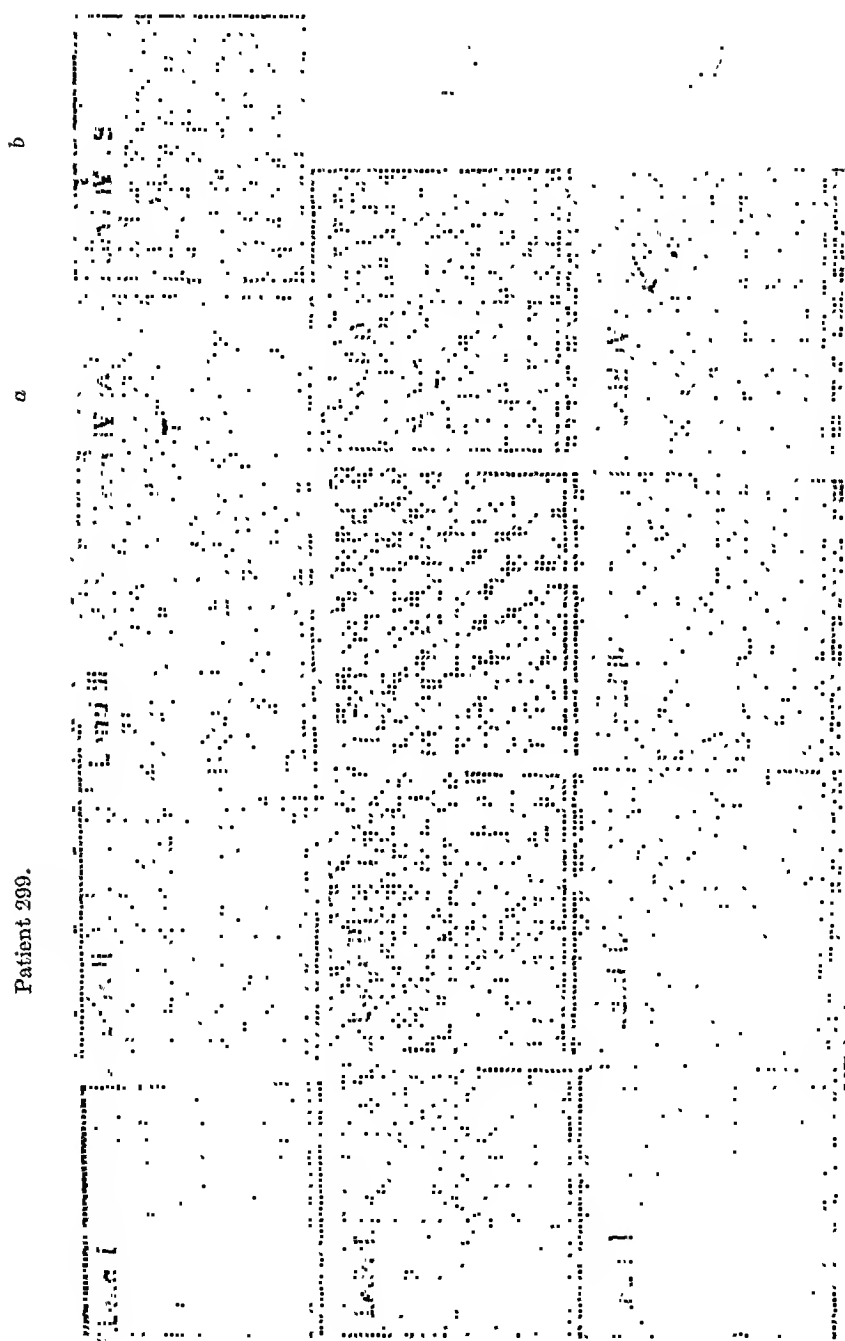


FIG. 3.—Cases of acute coronary occlusion, showing normal and abnormal Lead IV.

Table 2 shows that in these 40 cases there is practically no deviation in the width or height from the complexes of the 25 nor-

mal control patients. By "positive history" in the table is meant subjective complaints of precordial pain, with or without radiation, dyspnea, and other classical symptoms. By "routine leads" is meant findings in Leads I, II and III sufficiently characteristic to



FIG. 4.—Serial electrocardiograms in a case of acute coronary occlusion showing a persistently abnormal Lead IV.

make the electrocardiogram positive for myocardial damage due to coronary artery disease. A "plus sign" under Lead IV indicates some abnormal finding, making this lead of value in substantiating the clinical diagnosis.

Routine Leads I, II and III are to be considered positive only where the following findings are present: A high take-off of the *T* waves above the isoelectric line; diphasic *T* waves in more than 1 lead; slurring of the *Q-R-S* complexes in all leads; small complexes in all leads; and a deep *Q*<sub>s</sub> wave, the value of which as a positive finding we<sup>6</sup> recently emphasized.

Lead IV is to be considered abnormal when it varies from Lead IV in the control series, either in the direction of the complexes, as marked slurring of the *Q-R-S* complexes (Fig. 2, Case 491), also when *Q* or *T* waves are absent (Fig. 2, Case 492) or when there is an upright *T* wave (Fig. 2, Case 421). Slurring of the *Q-R-S* complexes in Lead IV is indicative of a lesion, since it is not always found in routine Leads I, II and III. In 5 cases, slurring of the *Q-R-S* complexes is present in all 4 leads, while in 5 it is present only in Lead IV. The diphasic *T* wave in Lead IV (Case 324, Fig. 2) is not to be considered abnormal, since it is also encountered in Lead IV of normal patients (Case 332, Fig. 1). An inverted *T* wave to 9 mm. in depth is not considered pathologic, inasmuch as it is found in normal cases. The average depth in these cases of the inverted *T* wave is 3.4 mm. Katz and Kissin consider inverted *T* waves of 9 mm. or more as pathologic, but since we encountered inverted *T* waves of 9-mm. depth in both normal and abnormal cases, we regard it as a doubtful indication of a lesion.

Of the 40 cases of coronary artery disease with myocardial damage, the routine 3 leads are positive in 28 cases (70 per cent). Twelve cases show an abnormality in Lead IV and positive routine 3 leads (30 per cent). Three cases, however (Nos. 433, 438 and 492, Table 2) show an abnormal Lead IV, but negative Leads I, II and III (7.5 per cent). The diagnosis of coronary artery disease with myocardial damage is, therefore, definitely aided by Lead IV in 7.5 per cent of cases.

**Non-coronary Cardiac Cases.** Eight cases of non-coronary cardiac disease were studied, 3 of whom were cases of mitral valvular disease (rheumatic), 2 auricular fibrillation (hypertensive), 1 intraventricular block and 1 hyperthyroid. In this group, Lead IV shows nothing of significance. This is interesting, as Hoffer and Delong reported abnormal Lead IV in a case of rheumatic mitral stenosis and in a luetic cardiac case.

**Lead IV in Acute Coronary Occlusion.** Thirteen of our series were first seen at the bedside at home during or within the first few days of an acute attack of coronary thrombosis. The history as well as the clinical symptoms and signs were characteristic, so that there was no question as to the clinical diagnosis. The electrocardiogram substantiated the diagnosis of the presence of the so-called coronary *T* wave of Purdee<sup>6</sup> or the cove *T* wave as described by Rothschild, Mann and Oppenheimer.<sup>7</sup> These criteria have been utilized as designating the routine 3 leads as positive (Table 3), in substantiat-

TABLE 3.—THE EVALUATION OF LEAD IV AND ROUTINE THREE LEADS IN CASES OF ACUTE CORONARY THROMBOSIS.

Case No.	Height of P waves, mm.	P-R interval, sec.	Q complex, mm.	Q-R-S complex.		T waves, mm.	Blood pressure.	Lead I.	Lead II.	Lead III.	History.	Evaluation of routine leads.	Lead IV.
				Height, mm.	Width, sec.								
172	-1	0.12	0	+10	0.08	+3	110/80	T <sub>1</sub> diphasic	T <sub>2</sub> diphasic	T <sub>3</sub> above		+	+
190	+2	0.16	-16	+15	0.08	-7	120/80	T <sub>1</sub> above	T <sub>2</sub> above	Slurred		+	-
299	-1	0.12	-15	+10	0.08	-10	90/60	T <sub>1</sub> above	T <sub>2</sub> above	T <sub>3</sub> inverted		+	+
350	-1	0.12	-11	+15	0.08	-8	90/60	T <sub>1</sub> above	T <sub>2</sub> above	T <sub>3</sub> inverted		+	+
362	-1	0.12	-6	+14	0.08	-7	90/60	T <sub>1</sub> above	T <sub>2</sub> above	T <sub>3</sub> cove		+	+
371	-1	0.12	-6	+10	0.08	+3	100/70	T <sub>1</sub> inverted	T <sub>2</sub> high	T <sub>3</sub> high		+	+
374	0	0.16	0	+5	0.08	0	120/80	T <sub>1</sub> upright	T <sub>2</sub> upright	T <sub>3</sub> diphasic		+	+
400	0	0.12	0	+9	0.08	+4	120/70	T <sub>1</sub> cove	T <sub>2</sub> cove	Slurred		+	+
422	+1	0.12	-6	+7	0.08	+3	150/100	T <sub>1</sub> diphasic	T <sub>2</sub> diphasic	T <sub>3</sub> inverted		+	+
427	+1	0.12	-2	+0	0.04	+2	136/80	Poor	T <sub>2</sub> above	Q <sub>3</sub> deep		+	+
485	-1	0.12	0	+13	0.08	+6	130/90	T <sub>1</sub> inverted	T <sub>2</sub> above	T <sub>3</sub> above		+	+
489	-1	0.16	0	+17	0.08	+3	100/74	T <sub>1</sub> inverted	T <sub>2</sub> absent	T <sub>3</sub> upright		+	+
504	-1	0.16	0	+4	0.08	+3	80/50	Slurring	T <sub>2</sub> inverted	Slurring		-	+
Av.	-0.30	0.12	-6.2	+11	0.073	+3							

ing the clinical diagnosis of acute coronary occlusion. Inverted or diphasic *T* waves do not seem sufficient to designate the routine leads as "positive" for acute coronary occlusion. In 9 of the 13 cases (69 per cent), the routine 3 leads are positive for acute coronary occlusion. Lead IV shows evidence of some abnormality in the remaining 4 cases (Cases 374, 422, 489, and 504 Table 3), namely, marked slurring of the *Q-R-S* complexes, upwardly directed *T* waves or an absent *Q* wave. In the 3 cases of acute coronary thrombosis (Cases 190, 299 and 350, Table 3), where Lead IV is negative, the complexes are similar in form to those found in normal Lead IV cases.

Fig. 4, Case 400, represents a serial electrocardiogram; 400*A* shows a definite cove *T* wave in Leads I and II, taken 24 hours after the onset of the acute attack. Lead IV shows slight slurring of the *Q-R-S* complexes and a definitely upwardly directed *T* wave. Following this case, it is apparent that the cove *T* wave disappears and becomes inverted in Leads I and II (Case 400*B*). On the other hand, Lead IV shows a persistently upwardly directed *T* wave, with a more pronounced slurring of the *Q-R-S* complexes. On the basis of the tracing in Case 400*C*, one would be justified in stating that only in Lead IV is there evidence of recent acute coronary occlusion, the routine 3 leads being negative. Thus it is shown by this serial electrocardiogram that an abnormal Lead IV can persist long after the disappearance of abnormal findings in routine 3 leads.

**Summary and Conclusion.** In 86 cases, Lead IV was studied in addition to the routine 3 leads, in both the anteroposterior and posteroanterior position.

A group of 25 normal cases shows a normal Lead IV to consist of a diphasic *Q-R-S* complex, with a definite deep *Q* wave. The *T* wave is inverted to the extent of 9 mm. and the normal Lead IV usually shows the *T* wave to be negative in the anteroposterior position; in 2 of our cases it was diphasic.

Deviation from a normal Lead IV consists in an absent *Q* wave, marked slurring of the *Q-R-S* complexes, absent or upwardly directed *T* waves.

A group of 40 cases of coronary artery disease with myocardial damage shows positive routine 3 leads in 28 cases (70 per cent); 12 show an abnormality in Lead IV and positive routine 3 leads (30 per cent); 3 (7.5 per cent) show abnormality only in Lead IV.

Four of 13 cases of acute coronary thrombosis (30 per cent) show an abnormal Lead IV, whereas the routine 3 leads are negative.

A serial study of a case of coronary thrombosis shows that abnormal Lead IV may persist long after abnormal changes have disappeared from routine 3 leads.

Since abnormal Lead IV proves positive in cases of coronary artery disease (7.5 per cent) and acute coronary thrombosis (30 per



cent), its employment as a routine electrocardiographic method both in private and hospital practice is advocated. The method carried out in this series was that of Wolferth and Wood, although in a few cases the posteroanterior position was also used and proved of value.

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### ON THE USE OF HEAT, DESICCATION AND OXYGEN IN THE LOCAL TREATMENT OF ADVANCED PERIPHERAL VASCULAR DISEASE.

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THE purpose of this paper\* is to report the results of applying three therapeutic procedures, heat, desiccation and oxygen in the problem of treatment of advanced peripheral disease. Physiologic considerations and the experience gained point to their potential value. Gradually developing organic occlusion of a vessel is often compensated by the development of collateral circulation and by canalization of the occluded lumen. But, the circulation to an extremity may be diminished suddenly, as by thrombosis in a previously diseased main artery, and a critical period of acute ischemia results, accompanied by pain, indolent ulcers, or gangrene. This paper is concerned with such cases, and the aim of conservative treatment is to keep the part alive or to minimize the area of gangrene until collateral circulation is established.

*Heat.* When heat is applied by the usual heated cradle to the feet of a person afflicted with advanced peripheral vascular disease, pain may be relieved, but often it is intensified. Since these obser-

\* Preliminary reports on certain phases of this work have appeared as follows: Starr, I., Jr.: A Thermoregulated Foot Cradle for the Treatment of Peripheral Vascular Disease, *Proc. Soc. Exp. Biol. and Med.*, 1931, 29, 166; On the Conservative Treatment of Gangrene of the Feet by a Selected Temperature, Oxygen and Desiccation, *Trans. Assn. Am. Phys.*, 1932, 47, 339. The first design of thermoregulated foot cradle was shown in the scientific exhibit of the American Medical Association, Philadelphia meeting, 1931.

vations were made when uncontrolled heat was applied, it seemed important to learn by experiment the range of temperatures in which the greatest degree of relief from pain is secured. Eleven patients with advanced peripheral vascular disease were chosen. All had gangrene; in only 1 (W. B.) was a pulse palpable in the vessels of the feet. In 6 of these, the diseased feet were placed in a water-bath at 25° C., and the temperature of this raised at the rate of 1° in 5 minutes. In 5, the presence of open lesions made prolonged immersion in water undesirable, and in these a similar experiment was performed by warming the air about the feet, the skin temperature being recorded by thermal junctions in 2 instances. The color of the skin was compared with those of Lewis' scale.<sup>2</sup> At temperatures under 30° C., the feet showed degrees of cyanosis, which varied in different locations, and the majority of the patients complained of pain. As the temperature rose, pain diminished or disappeared and the color of the feet improved, though it did not reach the normal in most locations. But at higher temperatures the feet usually became bluer and pain, if present before, returned. The optimum environmental temperature for relief of pain was found to be 33° to 35° C. (Table 1). This is approximately the same as that of the skin of normal feet when the vessels are fully dilated.<sup>3</sup>

TABLE 1.—PERIPHERAL VASCULAR DISEASE. DETERMINATION OF THE OPTIMUM TEMPERATURE.

Patient.	Diagnosis.	Kind of bath, water or air.	Temp. of free- dom from pain, ° C.	Temp. of best color, ° C.
<i>I. Patients Suffering From Pain.</i>				
C. W. . .	Diabetic gangrene of 1 toe	W	35 to 36	35 to 36
J. R. . .	Diabetic gangrene of 1 toe	W	32 to 35	33 to 34
M. A. . .	Diabetic gangrene of 1 toe	W	34 to 35	34 to 35
G. S. . .	Aortic thrombosis; endarteritis; gangrene of 2 toes	A	33 to 37	35 to 38
A. S. . .	Diabetic gangrene of 1 toe	A	27 to 35	31 to 34
C. G. . .	Diabetic gangrene of 1 toe	A	30 to 37	31 to 39
J. N. . .	Buerger's disease, gangrene of 1 toe; tip amputated	A	33 to 35	34 to 53
<i>II. Patients Without Pain (Sensation Impaired).</i>				
A. S. . .	Diabetes; 2 toes infected	W	....	34.5 to 40
W. B. . .	Diabetes; 1 toe amputated, 3 infected	W	....	37.5 to 40
D. F. . .	Diabetes; intermittent claudication	W	....	22 to 38
F. T. . .	Diabetes; great toe amputated; unhealed	A	....	33.5 to 35.5

The changes in color with changing temperature may be interpreted according to well-known physiologic conceptions. Because of the reduced circulation, the patient's ability to maintain the tem-

perature of his feet against that of the environment is impaired. A cool environment reduces the tissue temperature and so causes vasoconstriction and blueness analogous to that seen in normal persons exposed to more severe cold. On the other hand, a hot environment raises the tissue temperature and so causes increased tissue metabolism and demand for oxygen. The increase in circulation which would normally follow is prevented by the vascular disease, so blueness again results.

TABLE 2.—PERIPHERAL VASCULAR DISEASE. EFFECT OF INCREASED OXYGEN CONCENTRATION.

Patient.	Diagnosis.	Oxygen, per cent.	Color.	Sensation.
H. K.	Rheumatic heart disease; embolism; gangrene of both legs	21 80	XI V	Severe pain. Complete relief.
J. N.	Buerger's disease	21 80	X VII	Uncomfortable. Partly relieved.
A. S.	Diabetic gangrene of great toe	21 80	XI X	Severe pain. Went to sleep.
G. S.	Aortic thrombosis; endarteritis; gan- grene of 2 toes	21 84	XV VI	Severe pain. Sleeping.
A. S.	Diabetes; chronic ulcer	21 87	VIII VII	No pain. No pain.
C. G.	Diabetes, gangrene of great toe	21 80	X VIII	No pain. No pain.
W. B.	Diabetic gangrene; 1 toe amputated, 3 infected	21 78	XI IX	No pain. No pain.
S. J.	Arteriosclerotic gangrene, with small patches on toe and heel	21 90	XII X	No pain. No pain.
W. J.	Buerger's disease	21 89	XIII XI	No pain. No pain.

The colors are recorded by the Roman numerals used in the Lewis scale.<sup>2</sup> The brilliant red of reactive hyperemia is recorded as V, the most intense cyanosis as XVI. Intermediate colors are numbered correspondingly. The color of normal skin over the knuckles is usually VII. The colors here recorded represent the maximum changes observed.

*Oxygen, Locally Applied.* It has been demonstrated that oxygen can penetrate the human skin.<sup>4,5</sup> We were also aware that E. D. Churchill had employed oxygen as a means of local treatment. In our experiments, the feet of 7 patients showing gangrene or other lesions were tested. The foot was placed in a jar equipped with a rubber cuff to make an air-tight joint about the leg. The temperature was kept constant while the oxygen concentration of the air within the jar was slowly raised. No change in color or sensation resulted from 50 per cent oxygen or lower. Concentrations above 80 per cent caused relief from pain and slowly developing change of color (Table 2). Some cyanotic areas became bright arterial red, others showed less change and in others the cyanosis persisted. The change was most marked when the feet were originally very blue. When originally red, as in the rubor of Buerger's disease,

the change was distinguishable with difficulty. In all these cases, the original color of the skin slowly returned when the oxygen in the jar was replaced by room air. No change in skin temperature accompanied the changes in color; hence the effect must have been due to penetration of oxygen into the blood and not to improved circulation. From the relief of pain which occurred, it would appear that lack of oxygen is one factor in the pain in gangrenous conditions.

*Desiccation.* When oxygen was applied locally, it was found necessary to prevent the undue accumulation of moisture within the gas-tight cover. It soon appeared that this desiccation alone was of distinct advantage in preventing the development of wet gangrene; it may also convert a wet into a dry gangrene and so prevent infection of the necrotic area.

*Apparatus.* The results of these experiments led us to design apparatus for the application of a controlled temperature, desiccation and oxygen to the feet of bed patients.

*A Thermoregulated Foot Cradle.* The ordinary foot cradle, somewhat enlarged, has been equipped with temperature-control apparatus and arranged so that air would circulate through it by convection (Fig. 1). An adjustable gas-filled mercury contact thermometer and relay were used at first. Later, less expensive bimetallic thermoregulators proved more durable, more easily regulated, but not quite as reliable. Their specifications are as follows: Differential,  $2^{\circ}$  C. or less; range, approximately  $28^{\circ}$  to  $38^{\circ}$  C. or over; to operate on 110-volt a.c. or d.c. lines without other resistance; to break a current of 3 ampères without the use of a relay. A condenser, connected around the contact points, is desirable when direct current is used. Apparatus designed to regulate the temperature of water-baths, incubators, or to control the heating of houses will usually fill these requirements and may be obtained from many manufacturers. The list prices range from \$8 to \$15. In my experience, the more expensive types have had a more constant calibration and so have required less attention than the cheaper bimetallic thermoregulators.

The reliance on convection currents to circulate the air makes the temperature control far from perfect, and differences of from  $2^{\circ}$  to  $3^{\circ}$  C. may often be found in the air within the cradle. Larger differences occur if it is not well wrapped up with blankets. This degree of regulation seems good enough for clinical purposes, and mechanical stirring appears unnecessary.

*For the Local Application of Oxygen to the Feet.* Attempts to employ a simple method, as placing the foot within a rubber bag, failed because of the accumulation of moisture, the skin becoming macerated. So a smaller thermoregulated cradle (length, 24 inches; breadth, 17 inches; height, 12 inches) was surrounded by a sleeve-like cover of rubberized cloth, one end of which was bound firmly to the base of the cradle, the other bandaged loosely about the patient's thigh. A large celluloid window was inserted in this cover so that the foot and leg could be observed. The cradle design was modified from that of Fig. 1 in order to place all wiring and contacts outside the oxygen and so avoid the danger of fire.

When filled to a concentration of 50 to 80 per cent oxygen, the loss amounted to from 5 to 10 per cent an hour. Fresh oxygen was admitted 3 or 4 times a day, analyses being made before and after each addition. From 60 to 80 per cent oxygen was usually required to maintain the leg at its best color.

*For Desiccation.* Pans containing granular calcium chloride were placed under the lights of the thermoregulated cradle. A shelf of copper gauze was placed above the lights (Fig. 1). On this, lumps of  $\text{CaCl}_2$  were scattered, so that the warmed air on rising passed among them. By this means the relative humidity could be kept down to about 55 to 65 per cent in damp weather. In winter the artificial heating so reduces the humidity of the ward air that a much lower figure can be attained. Over 50 cc. of water has been collected in the desiccators daily in certain cases.

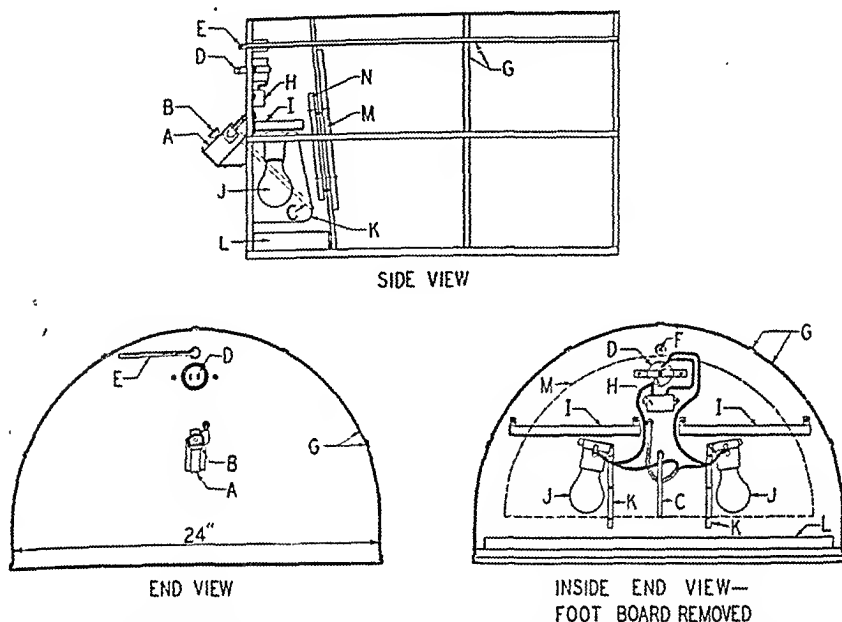


FIG. 1.—Thermoregulated foot cradle. Drawn to scale. Length, 2 feet; max. width, 2 feet; max. height,  $1\frac{1}{2}$  feet. A, Thermostat; B, thermostat regulating knob; C, bimetallic thermostat element; D, male attachment plug (female attachment on cord); E, thermometer stem; F, thermometer bulb; G, cradle frame (main framework of round-edge iron strip  $\frac{1}{4}$  by  $\frac{3}{8}$  inch, other pieces  $\frac{1}{4}$  by  $\frac{3}{8}$  inch, joints welded); H, condenser for d.c. current (not used on a.c.); I, screen for  $\text{CaCl}_2$ , of copper gauze; J, lamp; K, lamp shield and support, of galvanized iron sheet; L, pan for  $\text{CaCl}_2$ ; M, footboard, of  $\frac{3}{8}$ -inch 3-ply birch; N, cleat for footboard (it also shields footboard from direct light rays and possible overheating). When in use, the cradle is wrapped up in 3 or 4 layers of blankets; 15- or 25-watt lamps will usually give sufficient heat. The cradle shown is large enough to admit both feet and small enough to be easily transported in a passenger automobile. If the cradle is to remain in the hospital, it may be advantageously constructed with greater width so that it covers the entire foot of the bed.

**Clinical Methods and Results.** Thirty-five consecutive patients with advanced peripheral vascular disease have been treated in the medical wards. In all, there was a serious question whether amputation was not inevitable. The diagnoses and local findings have been given in Table 3, p. 505. The marked degree of impairment of circulation is further indicated by the fact that in only 2 cases (J. B. and W. B.) did the histamin puncture<sup>1</sup> on the dorsum of the foot cause a wheal or flare.

In addition to the three methods of treatment which were the particular subject of this study, the usual well-recognized procedures were employed. These included rest of the part, surgical treatment of open lesions and the careful management of diabetes when this was present. For this reason one must be particularly cautious in attributing results to any one or other of the means employed.

In most cases, the diseased foot was first placed in an ordinary foot cradle containing an electric bulb. After 24 to 48 hours, the thermoregulated cradle was substituted. If pain was not relieved within a few days, other procedures were tried in certain cases. These included the vasodilator drugs, acetyl- $\beta$ -methylcholin or sodium nitrite, oxygen in a few cases and nerve block. Only when conservative measures failed was amputation performed.

When the *thermoregulated cradle* was used, the initial temperature was usually 34° C. When necessary for the maximum comfort of the patient, the temperature was changed. The foot was kept in the cradle continuously until the acute condition had subsided.

All the patients agreed that greater comfort was secured from the use of the thermoregulated cradle than from either the unregulated or the unheated type. In about  $\frac{1}{2}$  the cases, relief was complete after a few days in the regulated heat. The cases not completely relieved fell largely into two definite groups: those with rapidly advancing gangrene and those with retained infection. The latter often had complete relief after the infection was drained. Therefore, very few of our cases required any sedative, only 2 required nerve block, and in none did severity of pain force amputation. This contrasts strongly with our previous experience in which the inability to control pain was so often the factor which drove the patient to accept amputation. Therefore, we have no doubt that the controlled heating relieves pain.

Our data on the effect of controlled heat on healing are also suggestive. In 2 cases of diabetes (W. B. and F. T.), toes had been amputated, but healing had not occurred under hospital treatment of 2 and 4 months respectively; it did occur slowly after the legs had been placed in a thermoregulated cradle. In several cases, indolent lesions began to heal when the cradle was applied, but in other cases no such stimulation of healing was observed. In 2 elderly patients, in whom gangrenous areas were removed below the line of demarcation (see below), contrary to expectation, healing of the stump occurred while the thermoregulated cradle was employed.

Application of 50 to 80% *oxygen*, together with regulated heat, has been tested in 4 cases only; in these the conditions were so severe that loss of both legs was threatened and operative risk excessive. All had advancing gangrene and suffered intense pain. In only 1 was there any suggestion that advance of the gangrene was delayed. There was, however, a change in color in every case, together with definite partial relief of pain. This was seen especially clearly in

1 instance in which the oxygen application was faulty. The pain became more severe when the oxygen leaked out and lessened whenever more oxygen was added. In the other cases, the effect on pain was indicated by the reduction in the dosage of sedative drugs which was possible during the use of oxygen.

*Desiccation* was used whenever frank gangrene was present. When open infections were present, it caused crusting and interference with drainage. In the first case treated, the gangrenous toe dried up and hardened except in the area of contact with the next toe. Here wet gangrene developed, at the only spot to which the dry air had no access. In the subsequent 14 cases, the toes being kept apart, the gangrenous areas become mummified and shrivelled to half their original size, the surface becoming as hard as a golf ball. Even though blebs formed, the moisture dried up so quickly that sloughing and infection did not follow. This will be illustrated in the cases given below.

In order to put these methods to more severe test, they were given a prolonged trial in certain cases in which high amputation is the accepted method of treatment but in which, because of complications, the operation involved unusual risk. These cases will be reported in detail together with one in which the results which followed the use of an unregulated cradle contrast strongly with those which followed the application of controlled heat.

**Case Reports.** CASE 1.—Mrs. H. K., aged 21, with rheumatic heart disease since childhood, became decompensated after Cesarean section. She improved for 6 weeks, but suddenly had an embolus into the right leg followed 3 days later by a similar catastrophe in the left leg.

On admission she showed the signs of a greatly enlarged heart, auricular fibrillation, mitral stenosis and pronounced aortic regurgitation. The legs were cold and edematous, with mottled cyanosis below mid-leg. No pulsation could be felt below the popliteal spaces. The pain in the legs was agonizing in spite of large doses of morphin.

Digitalis was continued in full doses throughout her illness.

The more painful leg (right) was put in the thermoregulated cradle, which was filled with oxygen and desiccated by calcium chloride; the left was put into the usual cradle warmed by a single bulb. The right leg became a much better color, many areas turning bright red, and pain in it largely disappeared. She still suffered severely from the left leg. Two days later, the cradles were interchanged, with relief of pain and improvement in cyanosis of the leg within the regulated temperature and oxygen, but pain returned to the other leg. Two days later the apparatus was altered so that both legs could be placed within the regulated temperature and oxygen, and the relief was very great, morphin being needed only about once in 4 days.

Gangrene slowly ascended both legs at an equal rate, uninfluenced by the treatment employed. Blebs formed in the pregangrenous zone; they ruptured and the fluid dried up. The gangrenous areas shrivelled to about  $\frac{1}{2}$  the normal size of the part, and the surface became hard as a golf ball. From 40 to 50 cc. of water were collected by the desiccators each day at this stage. The line of demarcation eventually formed below both knees and the limb blackened, shrivelled and hardened up to that point. During the first month, the patient had no fever; the leukocytes, elevated on

TABLE 3.—SUMMARY OF CASE RECORDS.

Date.	Patient.	Age, years.	Diagnosis.	Local lesion on admission.	Pulses.		Limit of dependent rubor or cyanosis.	Local treatment.			Relief of pain, if any, in 3 days or less.	Remarks.
					Dorsalis pedis.	Post. tibial.		Temp. °C.	Oxy-gen.	Desiccation.		
Jan., 1931	C. W.	58	Diabetes	Ulcer of 1st toe	0	0	Ankle	34	—	—	Complete	Healed; leg well for 2 years.
Feb., 1933	C. W.	63	Diabetes	Ulcer of 1st toe	0	0	...	34	—	—	Complete	Healed slowly; leg well for 2 years, except for claudication.
Mar., 1931	E. A.	64	Diabetes	Gangrene spot on 1st toe	0	0	Ankle	34	—	—	Considerable	No healing; very weak; inoperable; died several months later.
Feb., 1931	J. R.	71	Diabetes	Infected 1st toe	0	0	½ dorsum	34	—	—	Almost complete	Healed slowly; relapsed in 3 mos. Gangrene ascended steadily; amputation in 10 days.
Dec., 1931	A. S.	74	Diabetes	Ulcer of heel; paronychia, 1st toe	0	0	Ankle	34	—	+	Very little	Gangrene ascended steadily; amputation in 10 days.
Dec., 1932	A. S.	..	Diabetes	Gangrene of 1st toe	0	0	...	34	—	—	Slight	Healed slowly; relapsed in 3 mos. Gangrene ascended steadily; amputation in 10 days.
July, 1931	F. T.	69	Diabetes	Unhealed amputation of toe	0	0	Toes	34	—	—	No pain	Healed slowly; well 1 year later.
Jan., 1932	W. B.	45	Diabetes	Gangrene, tip of 3d toe; unhealed amp. of 2d toe; infection of 1st and 4th toes of rt. foot	+	+	Toes	34	—	—	No pain	Healed slowly; well 18 mos. later. Case 4.
June, 1932	W. B.	57	Diabetes	3d degree burn, dorsum of left foot	+	+	...	34	—	+	No pain	Healed; well 1 year later.
April, 1932	C. G.	57	Diabetes; angina pectoris	Gangrene of 1st toe	0	0	Toes	34	—	+	Moderate	See Case 2.
May, 1932	M. B.	68	Diabetes	Gangrenous spot at base of 5th toe	+	0	Slight	34	—	—	Complete	Healed promptly; well 6 mos. later.
May, 1932	J. B.	44	Diabetes	Gangrenous spot on great toe	+	+	Ankle	33	—	—	Complete	Healed; well 1 year later.
Nov., 1932	H. S.	55	Diabetes	Gangrene of 3 toes	0	0	...	34	—	+	Slight	Amputation as soon as acidosis was controlled.
Dec., 1932	R. S.	60	Diabetes	Gangrene of 1st toe and dorsum	0	0	Ankle	34	—	+	None	Gangrene ascended rapidly; amputation after 3 days.
Dec., 1932	W. T.	65	Diabetes	Gangrene of 4th toe	0	0	Ankle	31	—	+	Slight	Gangrene ascended rapidly; amputation in 2 days.
Jan., 1933	L. G.	70	Diabetes	Gangrene of 1st and 2d toes and dorsum	0	0	Ankle	34	—	+	Slight	Gangrene ascended rapidly; amputation in 2 days.
Sept., 1932	C. B.	51	Diabetes	Blebs on each toe of right foot	0	0	...	33	—	+	Almost complete	Gangrene ascended rapidly; amputation in 2 days.
Jan., 1932	W. J.	58	Thr. ang. obl.	Sup. gangrene of 1st toe and heel	0	0	Ankle	30	—	—	Complete	Marked temporary improvement; reported return of trouble 3 mos. later; improved again.
Dec., 1932	W. J.	59	Thr. ang. obl.	Ulceration of 1st toe	0	0	Ankle	30	—	—	Complete	Healed quickly; no trouble for 10 months.
Feb., 1932	J. N.	26	Thr. ang. obl.	Unhealed amputations for gangrene of both 1st toes	0	0	Distal ½ dorsum	34	—	—	Very slight	Toe became gangrenous; low amputation.
Nov., 1932	H. C.	55	Thr. ang. obl.	Gangrene of 1st, 2d and 3d toes and adjacent dorsum	0	0	Ankle	30	—	+	Complete	Healed in 1 month; well 1 year later.
Mar., 1933	N. P.	37	Thr. ang. obl.	Gangrene of tip of 1st toe	0	0	Distal ½ dorsum	34	—	—	Almost complete	Gangrene extended steadily; amputation after 10 days.
Dec., 1932	E. K.	50	Raynaud's disease; polycythemia vera	Gangrenous spot on 5th toe	+	+	Ankle	32	—	—	Complete	Lesion débrided; healed slowly; pain returned, then disappeared. Healed in 1 month.
Nov., 1931	G. S.	42	Thrombosis, abdominal aorta	Gangrene of both feet	0	0	Ankle	36	+	+	Marked, but not complete	Legs amputated; died of gas bacillus infection; necropsy.
June, 1932	N. R.	23	Postpartum femoral thrombosis	Gangrene of right leg	0	0	Knee	34	+	+	Marked	Amputation when line of demarcation formed.
Jan., 1932	H. K.	21	Endocarditis; embolism of both legs	Gangrene of both legs	0	0	Knees	37	+	+	Great, but not complete	See Case 1.
June, 1932	F. K.	74	Arteriosclerosis	Gangrene of 1st right toe	0	0	½ dorsum	34	—	—	Almost complete	See Case 3.
Dec., 1932	N. P.	72	Arteriosclerosis	Discolored painful 1st toe	0	0	Toes	34	—	+	Complete	Restored to normal; well 6 months later.



admission, had fallen to normal and remained there. There was little pain, though restlessness and discomfort necessitated small doses of morphin ( $\frac{1}{8}$  grain) occasionally. Her general condition had improved.

The second month was characterized by deepening of the line of demarcation (Fig. 2) and the development of small areas of pyogenic infection in the exposed stumps. For the first time, the gas within the cradle became slightly foul. The abscesses ruptured and dried up and were succeeded by similar infections in other places. No fever nor leukocytosis was present at this stage, but the general condition became worse, edema of the buttocks became more marked, a bed sore formed and anemia increased. The serum proteins were found to be diminished (4.46 per cent). Ammonium chlorid and theocin were given without effect. Urea was followed by slight diuresis. The appetite was very poor, and restlessness rather than pain required the use of more morphin ( $\frac{1}{8}$  grain) 2 or 3 times a day.

By the beginning of the 3d month, there was frank sloughing in the line of demarcation, the air within the cradle became very foul and a more active policy was decided upon. The cradle and oxygen were abandoned. The stumps were débrided, and a few days later the gangrenous area was amputated below the line of demarcation by Dr. L. K. Ferguson, and

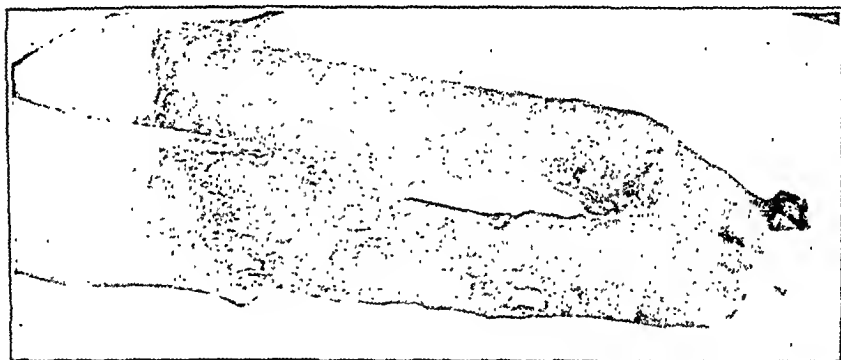


FIG. 2.—Legs of patient H. K., 6 weeks after the onset of gangrene.

maggots were applied to the stumps. These procedures caused no pain and required no anesthetic. They were followed by transient fever and leukocytosis which soon diminished. The stumps were quickly cleaned up by several applications of maggots and commenced to granulate nicely. But 2 weeks later, the patient's general condition became worse. Edema increased to the axilla, she became jaundiced and numerous bed sores developed. She died 3 months and 6 days after her admission. The stumps were clean and granulating when she died.

CASE 2.—C. G., aged 45, which had been diagnosed 5 years before admission, developed attacks of angina pectoris 5 months before. These occurred after less and less exertion until he suffered from them in bed. Two months before admission, the left great toe became painful, then gangrenous. Amputation was repeatedly advised but refused. He consented to come to the hospital only when assured that no amputation would be performed.

On admission, both lower extremities were edematous. The first left toe was gangrenous to the first joint; the line of demarcation was infected. When dependent, rubor covered the toes and extended over the dorsum at the base of the gangrenous toe. Histamin reaction showed neither wheal nor flare on the left dorsum. No pulsation could be felt below the left femoral; the radial arteries did not pulsate and the thickening and

beading of the palpable vessels were extreme. Roentgen ray showed calcification in all vessels of the lower extremities.

The diabetes was easily controlled without insulin. The diseased foot was put in a cradle set for 34° C. This was followed by almost complete relief of pain, but he continued to have attacks of angina almost daily. A week after admission, the gangrenous area was trimmed off with scissors and maggots applied to the stump on two occasions. After this, the attacks of angina became far less frequent, the general condition improved and the stump gave every evidence of healing. The improvement lasted about 10 days. Then a few red streaks were seen in the leg and this was followed by high fever; leukocytosis and signs of consolidation in the chest. He died in a few days. Necropsy was not permitted. The stump appeared to be in excellent condition at time of death, but that it was the source of an infected pulmonary embolus seems not unlikely.

CASE 3.—F. K., aged 74, had had angina pectoris for several years. For the last 6 months, the right foot had been cold, and swollen at night. Three weeks ago he noticed pain and tenderness in ball of the right first toe and found a draining sinus there. Soon a black spot appeared on the tip of this toe. It increased in size until it extended to the first joint. He was admitted, June 15, 1932.

Physical examination showed marked sclerosis of peripheral vessels. No pulsation could be felt below the popliteals. The tip of the toe was gangrenous and there was a draining sinus under the ball of the great toe. When hung down, redness extended to the ankle. The legs were thin and the skin shiny. Roentgen ray showed destructive osteomyelitis of terminal phalanx and first metatarsal of the gangrenous toe and gave evidence of sclerosis of the vessels of the foot.

The patient's foot was put in a cradle set at 34°, with CaCl<sub>2</sub>. Pain, which had prevented sleep when the old type of cradle was applied, was relieved almost completely. Pain returned one night when the thermo-regulated cradle was accidentally disconnected and was relieved when the connection was repaired. The gangrenous tip shrivelled and the line of demarcation did not advance. About 2 weeks later, the gangrenous area began to separate off and small infections developed in the fissure. These ruptured or were opened and dried up, but others kept developing. Two weeks later, redness and swelling began to extend to the dorsum. The gangrenous portion of the toe was then amputated by Dr. L. K. Ferguson below the line of demarcation without anesthesia. This proved to be more painful than had been expected. After this, all signs of extension of inflammation disappeared, though the foot became somewhat edematous. The stump did well, the anterior part closed in nicely, the healing of the lower part was held up by the sloughing tendon. Eventually maggots were applied to this area on 2 occasions. After this, the wound cleaned up nicely and healed slowly. Recovery was complicated by the appearance of a small abscess on the dorsum of the foot which was opened and drained, and eventually healed. For the last 6 months, the patient has been walking on his foot, his activity being limited only by his angina pectoris.

CASE 4.—W. B., aged 46. Diabetes had been known for 3 months before admission. At this time, the right second toe became painful, then gangrenous. One month later, the toe was amputated at another hospital where he was given insulin and his foot placed in an unregulated cradle. The wound failed to heal and the adjacent toes became involved; so, 2 months after the amputation, he was sent to the University Hospital.

On admission, pus exuded from the ball of the right great toe, the tips of the 3d and 4th toes were dusky and wrinkled, and pus could be expressed from them. Pus could likewise be expressed from the site of amputation. The foot was much swollen. The dorsalis pedis pulse was palpable but the

posterior tibial pulse was absent. There was redness of the toes when the foot was dependent. The histamin reaction showed a normal wheal but no flare on the foot. Sensation to pin prick, heat and cold and vibration was greatly impaired on the foot; that to touch was normal except on the toes. When the hands were placed in hot water, no change in the temperature of the toes occurred, indicating a high grade of organic obstruction to blood flow.<sup>6</sup> Roentgen ray showed that the head of the second metatarsal was rarefied and irregular and the rest of the bones in the anterior part of the foot showed marked osteoporosis. He had no pain at any time, doubtless due to the advanced neuritis.

The foot was placed in a cradle set to give 34° C. Wet dressings were applied and the toes débrided. This left the bones exposed on the tips of the 3d and 4th toes. After the infected areas had been well opened, no dressings were applied. The infections subsided slowly and in 2 months healing was complete. He has had no trouble with this foot in the 18 months since his discharge and has been working most of this time.

**Discussion and Summary.** The considerations which should govern the therapeutic application of heat in peripheral vascular disease are not identical with those which obtain in conditions in which the blood supply is normal. If the vessels are inadequate to carry sufficient blood to meet the increased oxygen demands of heated tissues, positive damage may result from degrees of heat which would be beneficial, were the blood supply more nearly normal. It is well known that "baking" a foot with undiagnosed peripheral vascular disease may cause gangrene: I have seen 3 instances. The possibility of damage from more moderate overheating may well be greater than has been realized. In the conditions under discussion, the ordinary foot cradle, covered with blankets and heated by one or more electric lights, is to be condemned because of the likelihood of overheating which it provides. In many cases, it causes unnecessary pain. Our experience indicates that the optimum temperature in peripheral vascular disease is from 30° to 34° C.; it is the temperature at which the tissues are accustomed to function. The physiologic method of treatment is to maintain this temperature by artificial means when the ability to do so naturally has been lost. While it is possible to accomplish this with the ordinary foot cradle, if careful attention is given to it, this result is far more easily and certainly attained by such a thermoregulated cradle as has been described. Evidence of its greater effectiveness in relief of pain and in promoting healing has been set forth.

Experience with the application of oxygen, together with controlled heat, has been insufficient to justify its advocacy as a routine element in treatment of peripheral vascular disease at the present time. Its use has been limited to very severe cases in which its contribution to the relief of pain was the only definite result.

Desiccation of the air within the thermoregulated foot cradle caused rapid drying of exposed gangrenous areas. It is a safe inference that it will prevent infection of such areas. It did not prevent

infection from forming in the line of demarcation when the gangrenous part began to separate.

The limitations of our methods can be seen by reference to Table 3. When relief of discomfort and cessation of the advance of lesions did not soon follow their application, we quickly turned to more radical procedures. The only deaths in the series have been described (Cases 1 and 2; and G. S., Table 3). Two cases, after having a functional restoration of their feet for 3 and 11 months, relapsed and came to amputation. Two others have had lesions return after initial recovery; both of these again did well under conservative methods. On the other hand, in 5 cases in which competent surgeons deemed amputation inevitable, the patients regained functional use of their limbs and have maintained it during the period of observation.

Therefore, we believe that these methods will form a useful supplement to other well-recognized means of treatment and that they may secure the recovery of certain cases which would otherwise come to amputation. In more severe cases, they may permit the continuance of conservative measures over longer periods of time without too much discomfort or danger. This will lead to new problems, some of which are already before us. The eventual solution of these problems might save much of the functioning tissue now lost because amputation must be performed so far above the level of the lesion.

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### A CONSTANT TEMPERATURE FOOT CRADLE.

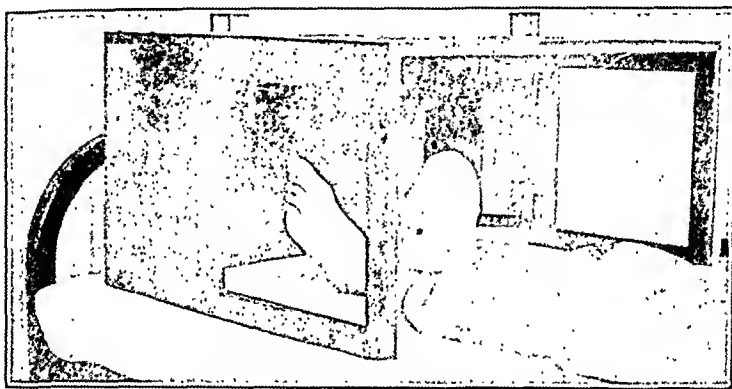
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TEMPERATURE control of the environment of the foot is desirable in cases of gangrene, thrombosis, ischemia from spasm or sclerosis, or of sepsis. The use of continuous warmth, combined with different types of dressings, is usually difficult because of the labor involved in frequent changes of hot-water bottles, and the danger of excessive heat from hot water or electric warm pads. Automatic and exact control is provided by a cradle described by Starr.<sup>1,2</sup> Personal communication with Dr. Starr led the author to build a cradle of

similar dimensions and design. This was so obviously helpful in improving the comfort and facilitating the healing of gangrenous lesions that further improvements were made. These have now been in use for a year with results that are gratifying to patients and to the medical staff members who have observed their use with diabetic gangrene, both dry and septic.

The original cradle of Starr was the conventional bed cradle of metal, covered with  $\frac{3}{8}$  inch mesh wire, and heated by an incandescent lamp which was placed in the remote end, behind a baffle board, to direct circulation of warm air and prevent contact burns. It was found necessary to cover the baffle board with a soft pad since it became too warm. The cradle was found to be unduly confining when employed continuously. Therefore a larger chamber was constructed, with dimensions allowing it to enclose both legs and feet comfortably. This was constructed of wood, and in one



Controlled temperature cradle in use, but with bed covers removed. (Note the glow of the lamp behind the baffle, the moist dressing on the right foot, and the availability of the feet for inspection.)

model the walls were made of two layers of ply-wood separated by about  $\frac{1}{2}$  inch air space to conserve heat. These chambers rest on the standard single hospital beds so that the covers are readily draped over them. Patients are more comfortable with them than with the covers resting on the feet. The temperature control adds further to the comfort of the patient.

Dr. Starr employed a thermostatic contact breaker and relay to control the lights. This is here substituted by a Ceneo-DeKhotinsky Thermo-regulator, obtained from the Central Scientific Co., Catalogue No. 13732. This is mounted so that the bimetallic element is suspended inside the cradle at about the height of the toes, while the adjusting knob is countersunk in the footboard of the cradle for ready regulating of the temperature. A small baffle board, perforated, keeps the feet from contact with the thermo-regulator. In the two corners of the cradle at the foot end are suspended two incandescant lamps, wired in series with the thermo-

regulator, and supplied from a detachable connector in the outside of the footboard. The lamps are separated from the cradle space proper by baffles made up of two layers of ply-wood separated by an air space. The foot cannot touch any hot or rough object inadvertently. This precaution is of prime importance. Temperature is measured by a Tycos bath thermometer which is suspended horizontally from one of the bars which form the top of the cradle. In one model it has been found convenient to hang a small thermometer in the chamber with the thermoregulator.

For convenience in changing dressings and inspecting feet the side panels are closed for only the first 10 inches. Also consideration of ease of storage and of handling led to hinging the top and side panels, so that the cradle, when not in use, folds to the size of a long suitcase, with no projecting equipment. When in use the cradle is 25 inches long, 32 inches wide, and 15 inches high.

The thermoregulator is sensitive enough to maintain temperature constant to within  $1^{\circ}\text{C}$ . The bath thermometers have been found accurate to within  $2^{\circ}\text{F}$ . In practice the temperature is adjusted to  $95^{\circ}\text{F}$ . and varied from that to suit the comfort of the individual. After the thermoregulator has been set it seldom needs further adjustment. It is wise to note the temperature daily to make certain that no accidental change of setting has been caused.

Experience has convinced those who have used it that the cradle is a comfortable and perfectly safe device, which has markedly facilitated the healing of lesions in the feet of a number of diabetics. The use of moist dressings in this cradle becomes at once the employment of continuous warm moisture with a minimum of nursing labor and no danger. The dressings are wrapped in oiled silk to reduce evaporation. When no dressings are employed the chamber is not warm enough to cause any uncomfortable dryness, although it is wise to use lanolin or cold cream on the skin. Current consumption is small. Two 40-watt bulbs are usually sufficient to maintain the temperature, when the bedclothing completely covers the cradle.

Since the preparation of this paper Dr. Starr has graciously submitted a copy of his most recent report on the use of heat, desiccation, and oxygen (preceding article). Our results agree very well with his, although no special efforts have been made to secure desiccation or to use oxygen. The larger air space may be responsible for the fact that we also have seen moist lesions drying without infection. Further protocols would add nothing but confirmation of the success Dr. Starr has described.

The author is indebted to Mr. J. R. Amaeker, Stanley, Wisconsin, for many of the improvements in the design and convenience of this device. He is prepared to build these cradles to order, completely equipped.

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## THE TREATMENT OF PELLAGRA WITH CERTAIN PREPARATIONS OF LIVER.\*

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MANY observers have noted that there is a close similarity in the symptoms of pellagra and pernicious anemia of the Addisonian type. However, the skin lesions in the one and the characteristic blood picture in the other serve to differentiate them.

Goldberger and Sebrell<sup>1</sup> have shown that daily doses of Liver Extract No. 343 (N.N.R.) by mouth will prevent and cure black tongue in dogs, a disease believed by some to be the analogue of pellagra. Liver and various extracts of liver, therefore, may be suitable agents for a more accurate analysis of the deficiency which brings about pellagra. Our purpose is to record preliminary observations on the effect of an oral and an intramuscular extract of liver in the treatment of pellagra.

**Method.** If not too far advanced, pellagrins usually recover when brought into a hospital and given a well-rounded diet. To study the effect of the liver preparations it was necessary to prepare a standardized diet similar to that upon which the patient developed the disease. In reviewing the foods consumed by our patients prior to their development of pellagra we were impressed with the similarity between their diets and the diet which Goldberger and Wheeler<sup>2</sup> used in producing pellagra in convicts in Mississippi (Table 1). In addition to the vitamin G (or B<sub>2</sub>) deficiency, Goldberger's original diet was lacking in vitamins A, C and D, and in iron, calcium, phosphorus, and complete proteins. A 2900-calorie diet† was prepared consisting of fat meat, field peas, rice, hominy grits, cane syrup, brown gravy, and lard. To supplement the vitamin,‡ mineral and protein deficiencies already mentioned, the patient received daily 90 cc. of cod liver oil, 45 cc. of tomato juice, 6 gm. of calcium gluconate, 6 gm. of iron and ammonium citrate, and

\* Presented before the Medical Section of the North Carolina State Medical Society on April 18, 1933, and before the American Society of Clinical Investigation on May 8, 1933.

† We are indebted to Dr. W. A. Perlzweig of the Department of Biochemistry and to Mrs. J. H. Martin of the Department of Dietetics for their coöperation in preparing this diet.

‡ We wish to thank Mrs. Susan G. Smith of the Department of Physiology for her assistance in planning the vitamin supplement.





60 gm. of cheese, given as medication on the wards. This diet was called Standard Basic Diet No. 1, being deficient only in vitamin G (or B<sub>2</sub>) (Table 2).

In this study, observations were confined to typical cases of pellagra with skin lesions, sore tongue, and gastro-intestinal disturbances. A total of 37 patients have been studied in detail, 23 of whom were given the Standard Basic Diet, and the remaining 14 given house diets as controls.

**Effect of Sunlight on Pellagra.** A marked improvement of the skin lesions occurred in 3 patients in the hospital on the Standard Basic Diet. A similar observation was made by Spies in 5 cases.<sup>3</sup> At the suggestion of Dr. H. L. Amoss these patients were exposed to direct sunlight to determine whether the disappearance of the lesions was due to the cure of the pellagra or to the protection from the sun afforded by the hospital. Three patients, receiving the Standard Basic Diet whose skin lesions had disappeared, were exposed to direct sunlight and developed the characteristic skin rash over the exposed areas.

**Case Reports.** CASE 1. (No. 5115).—R. S., a white male, aged 8, was admitted to the hospital May 1, 1931, with typical pellagrous lesions of the mouth, face, and hands. Beginning May 1, he was given the Standard Basic Diet No. 1, shown in Table 2. The lesions on the face and hands cleared rapidly during the following 6 days and by May 7 had practically disappeared.

Beginning May 7, the hands and feet were exposed to the direct rays of the sun for  $\frac{1}{2}$  hr. daily with the face protected by a wide brim hat. After 4 days of exposure, the face remained clear but the hands and feet were covered with new lesions. With the appearance of the skin lesions, the tongue and buccal mucosa became fiery red, and the patient had several large, liquid stools. On May 12, the exposure was discontinued and the patient was confined to the hospital. The Basic Diet was continued without the addition of any pellagra-curative factor and again by May 27, 15 days later, the lesions had disappeared and the tongue was normal. At this time, the hands were reexposed to sunlight  $\frac{1}{2}$  hr. daily for 5 days, and the lesions returned.

On June 2, the Basic Diet was discontinued and he was given a house diet which contained an abundance of pellagra-curative substances. The skin lesions disappeared, appetite improved, he became alert mentally, and was discharged as well on June 13.

CASE 2 (No. 13406).—A. R., a white female, aged 25, was admitted to the hospital on April 21, 1932, with diarrhea, nausea, vomiting, nervousness, sore tongue, and dermatitis of hands (Fig. 1). There was a mild secondary anemia, but gastric analysis showed normal acidity after histamin.

She was given the Standard Basic Diet No. 1 and the right hand and arm were exposed to direct sunlight for 30 min., the rest of the body being carefully protected. This exposure was repeated the next day for 60 min. A violent reaction with vesiculation resulted, and at the elbow a second-degree burn (Fig. 2). The rash on the arm which had been protected from the sun had almost disappeared during this interval. At the same time her general condition became very much worse; anorexia was marked; the diarrhea had increased to 18 stools per day; and the tongue became much more painful. The arm of a control patient exposed for a similar length of time showed only a mild erythema.

A commercial wheat germ flour (150 gm.) including some bran (Wheatone) was added to the diet daily. Although the lesion on the arm improved slowly, her condition remained the same or worse. On May 6, 10 days

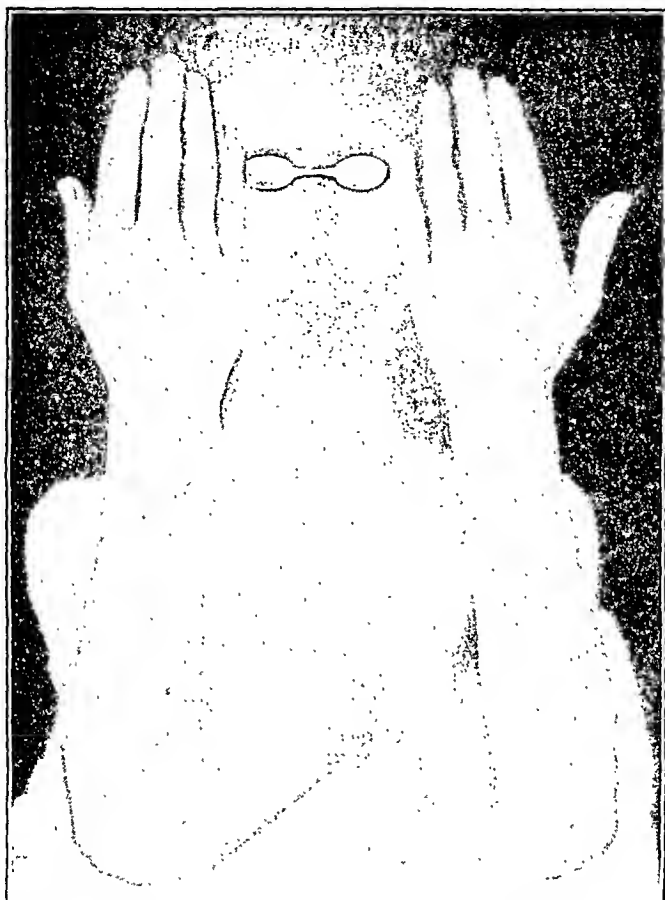


FIG. 1.—Case 2. Photographs of patient on admission to hospital showing slight dermatitis on hands and arms.

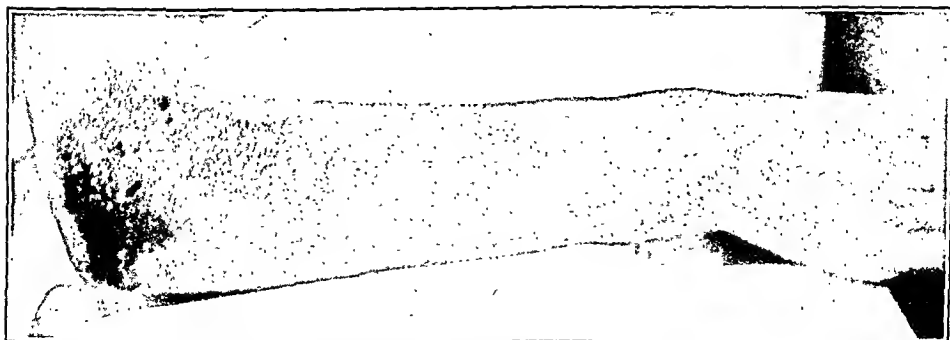


FIG. 2.—Case 2. Photograph showing extensive dermatitis on right hand and arm following exposure to sunshine.

after the last exposure to the sun, she was given a house diet and 90 cc. daily of an aqueous extract of liver by mouth. After 5 or 6 days a striking change was noted; the diarrhea had ceased; the tongue was no longer sore; the appetite improved; she began to gain in weight; and the skin lesions disappeared. She gained 5.5 kg. during the next 3 weeks. Beginning May 23, the right hand and arm were again exposed to the sun for 5 days, as before, and this time only a mild erythema, such as seen in a normal control, was observed (Fig. 3).

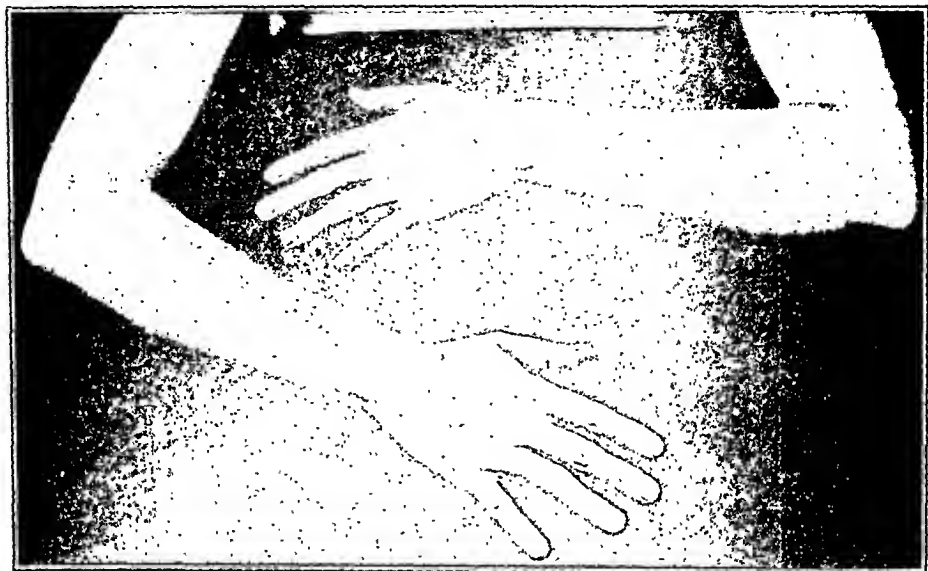


FIG. 3.—Case 2. Photograph showing absence of dermatitis following exposure to sunlight subsequent to administration of pellagra-curative substances.

Cases 1 and 2 illustrate the development of the characteristic skin lesions following exposure to sunlight, while subsisting upon Standard Basic Diet No. 1. Case 2 demonstrates that a unilateral dermatitis may be produced in pellagra by a unilateral exposure to sunlight. In Case 2 and in 9 other cases of pellagra the skin lesions did not recur after exposure to the direct rays of the sun, subsequent to the administration of pellagra-preventive substances.

**Effect of Oral Administration of An Aqueous Extract of Liver.** Ten patients with pellagra were fed the Standard Basic Diet for varying periods without improvement, and were then given 90 cc. of an aqueous extract of liver\* by mouth daily. Without exception a striking clinical improvement began between the 3d and 5th days, and continued until complete recovery.

**CASE 3 (No. 16778).—R. H.,** a white man, aged 66, was admitted to the hospital on July 29, 1932, with pellagrous lesions of the mouth, hands, arms and feet. He had a severe diarrhea and the feet presented marked secondary infection.

\* This extract, known as Valentine's Liver Extract E-29 was furnished through the courtesy of the Valentine Meat Juice Company. In this paper it will be referred to as "an aqueous extract of liver."

He was given the Standard Basic Diet No. 1 for several days with little change in his condition and then, following exposure to the sun, 30 min. a day for 2 days, he became rapidly worse with anorexia, increased diarrhea, and nausea and vomiting. Starting on August 1, he was given 90 cc. of an aqueous extract of liver by mouth daily. Five days later he began to improve and by the 10th day the diarrhea had subsided, the tongue was normal, the nausea and vomiting had stopped, and the dermatitis had almost disappeared. After 3 weeks of this treatment he had gained 6 kg. and was feeling entirely well (Chart I).

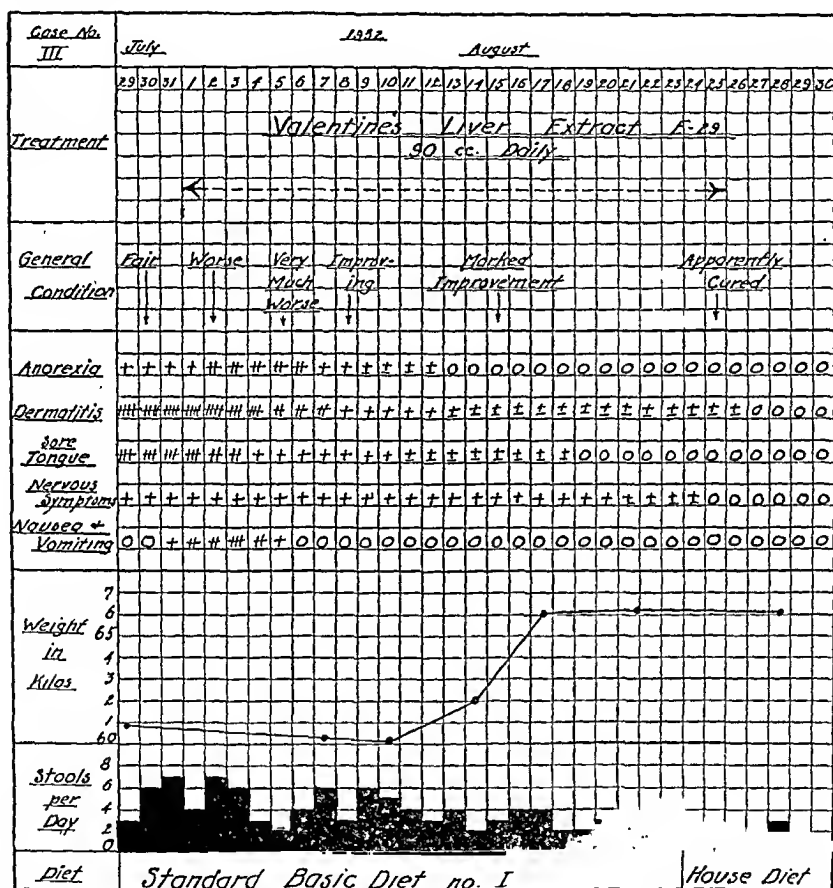


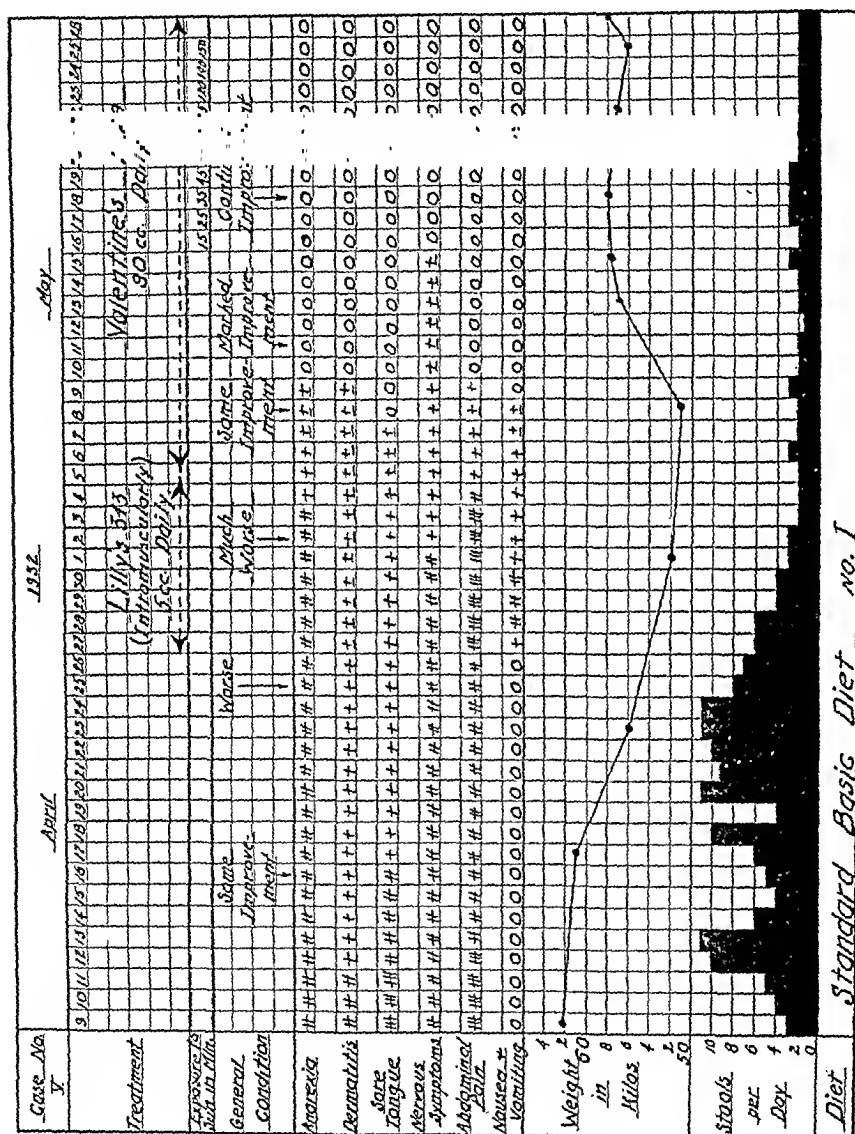
CHART I.—Chart from Case 3, showing symptomatology and result of treatment with an aqueous extract of liver, administered orally.

**Effect of Oral Administration of a Powdered Extract of Liver. CASE 4 (No. 5114).**—A. S., a white female, aged 26, was admitted to the hospital on May 1, 1931, with pellagrous lesions of mouth, hands, feet, and vulva.

Beginning May 1, she was given the Standard Basic Diet No. 1 supplemented by 3 vials of a powdered Liver Extract\* by mouth daily. (Each vial contained the extract derived from 100 gm. of fresh liver.) Improvement was noted in the lesions on the hands and feet 4 days after the treatment was started. By May 22, the oral and buccal lesions were healed and the dermatitis had completely disappeared from the hands, feet, and vulva.

\* Parke, Davis & Co.

Beginning May 22, one hand and arm were exposed to the direct sunlight for 15 min. each day and increasing to 1 hr. daily. After 7 days of exposure a normal healthy tan developed over the exposed area without evidence of dermatitis. The patient gained 3 kg. and was discharged in excellent condition on June 7.



CASE 5 (No. 13011).—T. I., a colored male, aged 49, was admitted to the hospital April 9, 1932, with the complaint of weakness, abdominal pain, diarrhea, sore mouth and rectum, and dermatitis of the hands.

Beginning April 9, the patient was given the Standard Basic Diet No. 1. The symptoms continued and the stools increased from 3 on April 9 to 11 on April 13, and then decreased to 5 on April 16, when he reported that he felt somewhat improved. The stools again increased to 11 per day by April 24, and all the other symptoms became aggravated. On April 25, he received two intravenous injections of calcium gluconate (10 cc. of 10% solution) and one injection on the following day. For 1 week, starting April 27, he received daily intramuscular injections of 5 cc. of Liver Extract No. 343. During this period his stools decreased, but all the other symptoms were aggravated and he developed nausea and vomiting so that this therapy was discontinued.

Beginning on May 6, he received 30 cc. of an aqueous extract of liver by mouth 3 times daily. Between the 3d and 6th day of the treatment the nausea and vomiting, abdominal pain, diarrhea, sore tongue, anorexia and dermatitis disappeared and he began to gain weight for the first time since admission. Exposure to direct sunlight for 4 days failed to produce skin lesions and he was discharged in good condition on May 29, 1932 (Chart II).

CASE 6 (No. 11803).—J. W., a white male, aged 21, was admitted to the hospital on May 9, 1932, with sore mouth, diarrhea, and dermatitis of hands and arms. The pellagra was complicated by a bilateral basal bronchiectasis and achlorhydria after histamin.

He was given the Standard Basic Diet No. 1 and 150 gm. of a commercial wheat germ (Wheatone) daily. The skin rash gradually subsided though his general condition became progressively worse with increased diarrhea, sore tongue, anorexia, and after 2 weeks, nausea and vomiting.

Beginning May 27, he was given daily 5 cc. of Liver Extract No. 343 intramuscularly. Very slight, if any, improvement was noted. The nausea, vomiting, diarrhea, and anorexia continued unabated. On June 3, 60 cc. of an aqueous extract of liver were given by mouth for 4 days and then increased to 90 cc. daily. Four days after instituting this therapy, the appetite improved rapidly; there was no further nausea and vomiting, and the tongue began to heal. The diarrhea subsided 8 days after starting this treatment. Beginning June 12, the right hand and arm were exposed to sunlight for 30, 40, 50 and 60 min. on successive days without recurrence of the skin rash. He gained weight rapidly and was discharged with no evidence of pellagra on July 11.

In these 2 cases and in 2 others treated in the same manner, little if any clinical improvement was observed during the period of intramuscular treatment with Liver Extract No. 343 in 5-cc. doses. These 4 patients promptly recovered when given 90 cc. of an aqueous extract of liver daily by mouth.

A 5th patient, who had shown no evidence of improvement with the intramuscular Liver Extract No. 343 in doses of 5 cc. daily, made a dramatic recovery after taking by mouth daily doses of the residue obtained from the alcoholic precipitation of 90 cc. of an aqueous extract of liver.\*

\* The addition of 95% alcohol to an aqueous extract of liver produces a precipitate which can be dissolved in water and given by mouth. This material was prepared for us by the Valentine Meat Juice Company.

**Discussion.** In order to determine the value of certain extracts of liver in the treatment of pellagra, a diet was prepared, similar to that which the patient had been taking prior to the development of symptoms. This Standard Basic Diet described above contains adequate amounts of proteins, fats, and carbohydrates, minerals and all the known vitamins except vitamin G ( $B_2$ ). Patients with pellagra reported in this series did not improve on this diet, and 3 out of 4 dogs partaking of this diet died of typical black tongue between the 25th and 45th day of the experiment.

It would seem that the disappearance of the skin lesion does not necessarily indicate a cure of the disease since the lesions can be reproduced by exposure to direct sunlight, unless the patient has been protected by some pellagra-curative substances. The failure of the patient to develop skin lesions after adequate exposure to sunlight furnishes an additional clinical test of the cure of the disease.

The evidence presented here indicates that the bilateral symmetry of the lesion is due to bilateral exposure to sunlight. In this series it has been shown that unilateral lesions can be produced by unilateral exposure (Figs. 1, 2, and 3).

Oral administration of an aqueous extract of liver in doses of 90 cc. daily effected a cure in 10 cases; a powdered extract of liver in doses of 3 vials daily in 1 case; and an insoluble residue derived from the alcoholic extraction of an aqueous extract of liver in 1 case.

Of the 14 patients given house diets as controls, 3 were far advanced cases and died even though they received an abundance of known pellagra-curative substances. The remaining 11 patients recovered, their clinical course being about the same as that group of patients receiving the Standard Basic Diet and the aqueous liver extract by mouth.

Ramsdell and Magness<sup>4</sup> have reported the recovery of 22 cases of pellagra treated with 2 cc. daily of Liver Extract No. 343 intramuscularly. Their patients received a general house diet, which undoubtedly contained a considerable amount of pellagra-curative substances. In the present series of 5 cases treated with Liver Extract No. 343 intramuscularly in doses of 5 cc. daily, there was little or no clinical improvement. This discrepancy is explained by the difference in the diets, since our basic diet contained practically no Vitamin G ( $B_2$ ).

It is of interest to note that yeast which cures pellagra<sup>5</sup> and black tongue in dogs<sup>6</sup> is ineffective in the treatment of pernicious anemia,<sup>7</sup> until it has been digested with normal gastric juice.<sup>8</sup> Since Spies<sup>9</sup> has shown that meat digested with the gastric juice of pellagrins with alcholhydria is effective in the treatment of pernicious anemia, it is probable that the deficiency in pellagra is entirely different from that in pernicious anemia.

**Summary.** 1. A diet has been prepared for the clinical study of pellagra which is adequate in all known nutritional elements except Vitamin G ( $B_2$ ).

2. Exposure to direct sunlight in North Carolina in the spring and summer months produces dermatitis in active and potentially active pellagrins, but not in normal controls or in pellagrins who have received adequate treatment.

3. Ten patients with active pellagra, subsisting upon a basic diet deficient in vitamin G ( $B_2$ ) showed satisfactory remission after the oral administration of 90 cc. daily of an aqueous extract of liver.

4. Five patients on the same basic diet showed little or no improvement when given Liver Extract No. 343 intramuscularly in doses of 5 cc. daily. When the oral aqueous extract of liver was substituted for the intramuscular extract, a dramatic clinical improvement began between the 3d and 5th days and continued until the patients were apparently well.

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### NEGATIVE RESULTS IN THE TREATMENT OF SICKLE-CELL ANEMIA.

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It is generally conceded that the treatment of sickle-cell anemia is unsatisfactory. A review of the literature, however, reveals that the evidence upon which to base a fair appraisal of treatment results is scant, and that there is difference of opinion as to the effectiveness of certain forms of therapy.

Sydenstricker,<sup>1</sup> Yater and Mollari,<sup>2</sup> Leivy and Schnabel,<sup>3</sup> and Anderson and Ware<sup>4</sup> failed to observe benefit in patients with severe sickle-cell anemia following the use of liver or liver extracts. "Marked improvement on liver therapy" was reported by Levy<sup>5</sup> in 3 patients with "active" sickle-cell anemia, but the diagnosis is open to question in 1 of his cases, and in the others the anemia was mild. Brandau<sup>6</sup> added fresh spleen to his patient's diet for 25 days, without improvement. Iron, arsenic, calcium, iodids, alkalies and



general supportive measures have been used without apparent benefit. Transfusion has proved to be of aid in relieving the acute symptoms, but its effect has been temporary. Torrance and Schnabel<sup>7</sup> observed prompt relief of pain following the use of potassium thiocyanate in combination with potassium citrate and bicarbonate of soda, but this like other symptomatic treatments that have been tried, did not alter the anemia or prevent the recurrence of symptoms. Splenectomy as a therapeutic measure has been recorded in nine instances. Accurate evaluation of the procedure is difficult at the present time because of the inadequacy of the observations and controls. Permanent improvement in the anemia or in the clinical picture following the removal of large spleens in childhood remains to be proved. The removal of atrophic spleens characteristic of the later stages of the disease is useless and may be impossible.<sup>8</sup>

Because the number of therapeutic experiments under controlled conditions has been few, treatment observations made on 7 patients with sickle-cell anemia are here recorded. All were negro patients at the Memphis General Hospital and all had in common jaundice of a hemolytic type, anemia with marked regenerative signs, sickled erythrocytes, leukocytosis, fever, enlarged heart with hemic murmur, palpable liver and non-palpable spleen. Six of the cases were of the chronic type, and gave a history of constitutional inferiority from birth, and of recurrent attacks of sickness characterized by weakness, fever and varied symptoms, of which headaches, vomiting, and pains in abdomen, bones or joints were outstanding. The 7th case was a child with the sickle-cell trait, observed during what was evidently her first anemic episode. For the sake of brevity, the details of the clinical record are omitted in this paper, and the reports limited to the therapy used, and the alterations in the blood picture that followed.

**Treatment Records.** CASE 1.—A. M. C., female, aged 18, has been jaundiced and anemic since infancy. During 4 years the erythrocyte counts have varied between 2,000,000 and 3,000,000, the hemoglobin between 6 and 9 gm., the reticulocytes between 10 and 20 per cent (Fig. 1). The anemia was of the microcytic, hypochromic, regenerative type. Typical sickled cells were always in the blood smears. Leukocytosis and thrombocytosis were constant. Free hydrochloric acid was found in small quantities in the gastric juice.

On the first hospital admission at 14, pills of ferrous carbonate, 1 gm., q. d., liver diet, and sodium cacodylate, 7.5 gr. every other day were given for 2 weeks. Clinically there was improvement, but the blood picture did not significantly change.

One year later, a 3-year-period of observation was started, during which time various antianemic measures were in succession tried, with control periods between the treatment experiments. The patient was a particularly favorable subject for investigation, for the anemia was marked, there were no evident complications and the patient faithfully reported week after week for blood studies. Except for short periods of debility, she was able to walk about a mile to and from the laboratory and do part-time work as a

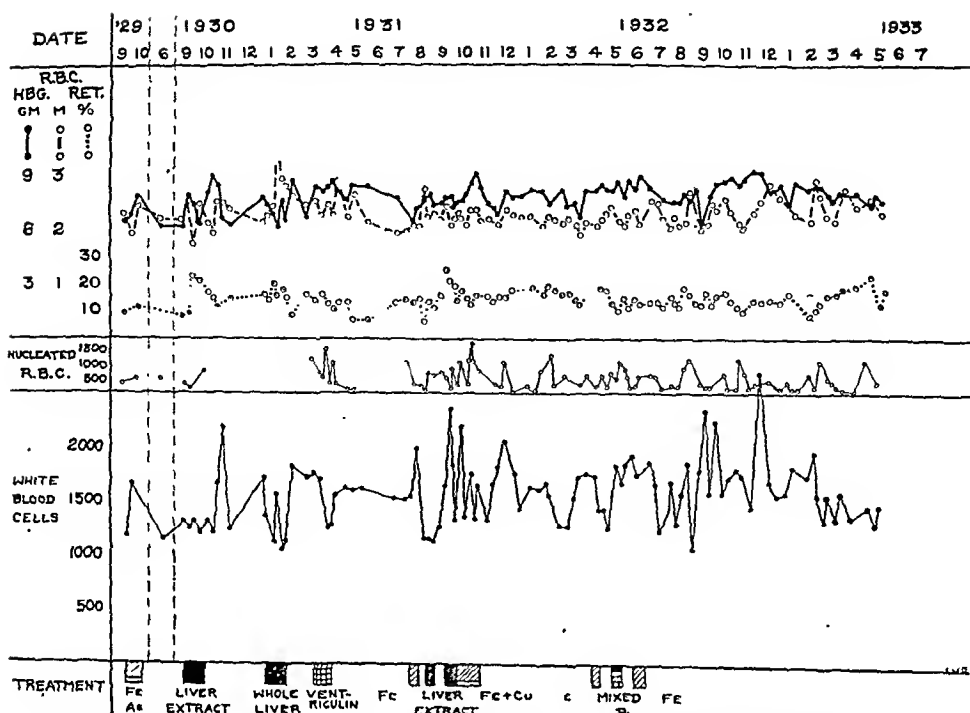


FIG. 1.—Case 1 (A. M. C.). Chart showing erythrocyte, hemoglobin, reticulocyte, nucleated red blood cell, and leukocyte values in relation to therapy.

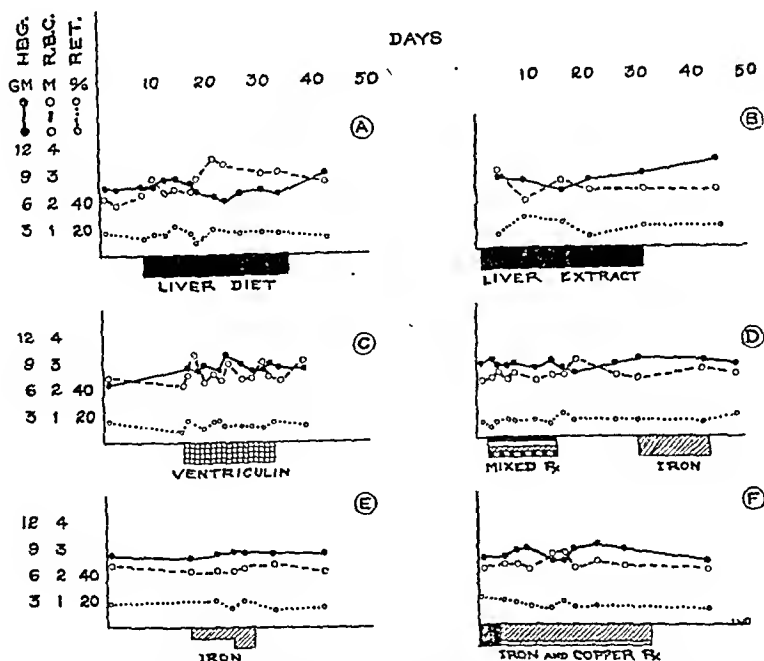


FIG. 2.—Case 1 (A. M. C.). Chart showing in more detail than in Fig. 1, the response of erythrocytes, hemoglobin and reticulocytes to various antianemic measures.



*Discussion.* The response of the anemia to the various anti-anemic measures used (Figs. 1, 2 and 3-A), reveals no significant alteration. The minor fluctuations in values for erythrocytes, nucleated red blood cells, reticulocytes, hemoglobin and leukocytes during the treatment periods are of the same magnitude as those observed during the control periods. The number of sickled cells in the stained smears, and the capacity of the erythrocytes to sickle in moist preparations were not affected by the therapy used. Clinical phenomena, such as attacks of joint pain, abdominal crises, leg ulcers, and mild respiratory infections occurred during the treatment periods as well as during the non-treatment intervals. The blood picture was essentially the same at the age of 14 when the patient was first admitted to the hospital as it was for the next 4 years. The anemia was no more severe when the patient was sick in bed or during attacks of severe pain, than when she was symptom free and working. This case is representative of a type of sickle-cell anemia in which the symptoms are subject to marked remissions and exacerbations, but the anemia is chronic and fixed within rather narrow limits.

CASE 2.—R. C., male, aged 11, was admitted during an attack of acute arthritic pains. The red cell count was 3,110,000, the hemoglobin 7.9 gm. and the reticulocyte percentage 9. Mixed treatment, j, 12 cc., was started, and 8 days later increased to 30 cc., q. d. which was continued for 24 days. Pills of ferrous carbonate 2 gm., q. d. were then added and the combined medication given for 29 days, following which liver diet, 200 gm., q. d. was substituted, and continued for 17 days. There was no appreciable effect of these therapeutic measures on the anemia, in fact there was a tendency for the anemia to become worse (Fig. 3-B). The patient had a draining osteomyelitis sinus and also had swollen cervical lymph nodes, probably tuberculous, and these complications are to be given consideration in evaluating the lack of response.

CASE 3.—A. M., male, aged 24. Following the subsidence of an attack of severe lumbar pain with associated abdominal tenderness and rigidity, the patient was given, in addition to the usual hospital diet, 400 gm. of whole liver per day for 26 days with no alteration in hemoglobin, red blood cells or reticulocytes (Fig. 3-D).

CASE 4.—C. T., male, aged 8, gave a typical history of sickle-cell anemia. The red blood cell count was 1,790,000, hemoglobin 7 gm. and reticulocytes 32 per cent. Following a 10-day treatment with alkalis without effect on the anemia, mixed treatment, j, 12 cc., q. d. was given for 9 days, after which the dosage was doubled and pills of ferrous carbonate 2 gm., q. d. were added. After 1 month's trial on this combined therapy, desiccated hog's stomach, v, 30 gm., q. d. was substituted and continued for 18 days. There was no appreciable effect of any of these drugs on the level of the anemia (Fig. 3-E). The slight increase in reticulocytes is probably not significant.

CASE 5.—P. M., male, aged 12, was admitted during an attack of lobar pneumonia. Large ulcers of 2 years' duration were present on both legs. The red blood cell count was 2,420,000, hemoglobin 6.7 gm., leukocyte count 19,900. The anemia was of the normocytic, normochromic type. Free hydrochloric acid was present in the stomach contents. With the exception of a temporary improvement following a transfusion of 275 cc. of blood, there was no alteration in the degree of anemia under general

hospital care and supportive measures, although the clinical condition steadily improved. The use for 19 days of a mixture of cod-liver oil, iron and bone-marrow extract, m, 12 cc., q. d. was without effect. Subcutaneous liver extract, c, 1 ampule q. d. for 21 days, supplemented by a high caloric diet which included whole liver, 300 gm., q. d. for 13 days, and followed by desiccated hog's stomach, v, 10 gm., q. d. for 12 days produced no change in the blood picture (Fig. 3-F).

CASE 6.—W. T., male, aged 28, was admitted with severe abdominal symptoms which rapidly subsided. The red blood cell count was 3,100,000, hemoglobin 7.8 gm., reticulocyte percentage 8.2. Whole liver 450 gm., q. d. was given for 12 days with no significant alteration in the blood findings.

CASE 7.—B. L. H., female, aged 3, was admitted because of marked weakness and cachexia associated with bronchopneumonia. The past history was essentially negative. The red blood cell count was 700,000, hemoglobin 4.1 gm., reticulocyte percentage 29; leukocyte count 64,000, which when corrected for megaloblasts and nucleated red blood cells was 21,200. Typical sickled cells were not present in the stained smears, but moist preparations on standing revealed the sickle-cell phenomenon. The sickle-cell trait was also demonstrated in the father and in two siblings. Free hydrochloric acid was present in the stomach contents.

On account of the severity of the anemia and the apparent critical condition of the patient, transfusion of 230 cc. of whole blood was given on the second day, and daily medication consisting of whole liver, 200 gm., liver extract, x, 45 cc., and iron and ammonium citrate 1.5 gm. was started. The patient's clinical condition rapidly improved, the red blood cell count and hemoglobin values rose and the reticulocyte count precipitately dropped (Fig. 3-C). Coincidentally the primitive cells of the erythrocytic and granulocytic series disappeared from the circulating blood, and the leukocyte count returned to normal (Fig. 3-C). On the 19th day of treatment, severe diarrhea developed and medication was discontinued. Improvement in the blood picture continued in absence of medication but soon reached a level of 3 to 4 million red blood cells and 9 to 11 gm. of hemoglobin, where it remained during the observation period. Further studies of the blood have not been possible.

*Discussion.* The favorable response following therapeutic measures in this case cannot be entirely attributed to the medications used, for there was no control period to indicate what would have happened had no medication been given, and the improvement in the respiratory infection rather than the antianemic measures used might have been the predominant factor in causing the return of the blood picture toward normal. This patient, whose anemia improved, differed from the 6 patients whose anemia remained stationary in that she was younger, the anemia was observed during its early stage, and typical sickled cells were absent in the stained smears. Cases of this type, which at one time give the characteristic picture of active sickle-cell anemia and then revert to a condition in which the sickle-cell trait is the only demonstrable abnormality are rare. The existence of such a type, and the possibility of spon-

m Myeladol (Upjohn). Each fluidounce contains: Cod liver oil 120 minims, glycerinated extract red bone marrow 10 minims, iron and ammonium citrate 4 gm., malt extract, q. s.

c Liver extract, subcutaneous (Chappel). Each ampule contains the active principle of 25 gm., of liver.

taneous remissions in any given case, should make one guarded in drawing conclusions as to the effectiveness of therapeutic measures.

**Summary.** Seven negro patients with sickle-cell anemia were treated with one or more of the following antianemic medications: whole liver, liver extract by mouth, liver extract subcutaneously, desiccated hog's stomach, bone-marrow extract, iron, and transfusion. In 6 cases the erythrocyte, hemoglobin and reticulocyte values, and the clinical condition following therapy did not significantly change. In 1 negro child with the sickle-cell trait, observed during an initial anemic crisis associated with bronchopneumonia, clinical improvement and improvement of the anemia followed transfusion and the administration of liver and iron.

There is a dearth of information concerning the natural course of sickle-cell anemia in all its varied manifestations, and the possibility of spontaneous remissions must be considered in the evaluation of favorable therapeutic responses. The effectiveness of any form of therapy in the treatment of sickle-cell anemia remains to be proved.

Appreciation is expressed to the clinical staff of the Memphis General Hospital for their cooperation, to Jaunita Bibb for technical assistance and to the manufacturers for furnishing without cost the drugs used in this investigation.

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## THE EFFECT OF LEUKOCYTIC CREAM INJECTIONS IN THE TREATMENT OF THE NEUTROPENIAS.

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THE purpose of this paper is to present a preliminary report of the effect of intramuscular injections of leukocytic cream in cases of severe neutropenias and to describe a method for the separation of the leukocytic cream from the blood.

Nuclein therapy to increase the germicidal power of the blood in infections was advocated in 1893 by Vaughan, Novy and McClintock<sup>1</sup> and from time to time contributions on this subject have appeared in

the literature (Ames and Huntley,<sup>2</sup> De Paoli and Calisti,<sup>3</sup> and others). The therapy of neutropenia has been excellently reviewed recently by Doan<sup>4</sup> who has given extensive references to the subject, which will not be repeated here. Observations by Sabin,<sup>5</sup> Sabin, Doan, Cunningham and Kindwall<sup>6</sup> and Doan and Zerfas<sup>7</sup> brought out the fact that showers in the peripheral circulation of old non-motile polymorphonuclear leukocytes are soon followed by an increase of young neutrophils. These findings lend support to the theory that normally stimulation to new granulocytic cell formation is due to material liberated from the breaking down of old cells. Very likely the beneficial effect of transfusions in neutropenias is due to the introduction in circulation of such material. I personally feel that in view of the findings to be reported here it might be better to limit the conception of the effect of autolytic products of old cells to the maturation and release of new granulocytic cells rather than the multiplication of parent cells.

Recently the most successful attempt in the treatment of neutropenias has undoubtedly been the introduction of pentose nucleotides by Jackson, Parker, Rinehart and Taylor<sup>8</sup> in 1931. This substance, now available commercially, has been rather extensively used. In 69 cases of agranulocytic angina, malignant neutropenias and allied conditions Jackson, Parker and Taylor<sup>9</sup> report that 74 per cent of the cases treated with nucleotides recovered. They believe that the preparation was effective because of the favorable clinical and hematologic changes about the 5th day of treatment, and because the subsequent hematologic improvement in practically all cases followed the same pattern. The mortality in the cases treated with nucleotides is certainly lower than that of any other form of treatment yet devised. Doan<sup>4</sup> reports the following table of mortality in malignant neutropenia or agranulocytosis:

TABLE 1.—MORTALITY STATISTICS OF MALIGNANT NEUTROPENIA.  
(DOAN.)

Therapy.	Cases.	Deaths.	Mortality per cent.
Untreated . . . . .	Many	...	90 or more
Miscellaneous therapeutic measures . . . . .	178	133	74
Arsphenamin . . . . .	33	24	72
Blood transfusion . . . . .	53	34	64
Irradiation . . . . .	64	34	53
Nucleotide . . . . .	44	11	25

It would be entirely beyond the purpose of this paper to discuss the mechanism of action of all of these therapeutic measures. I wish, however, to point out the probability that Roentgen ray acts upon the bone marrow not by direct stimulation but through the intermediate destruction of a number of cells and liberation of disintegration products. This view is supported by the fact that, in the majority of cases treated by Roentgen ray, after the application

there is first a further lowering of the level of the granulocytes, to be followed in the favorable cases by an increase. There are, however, many cases of neutropenia, both of the agranulocytic type and in acute leukemias, that following even a single dose never recover from the further depression of the bone-marrow function.

It occurred to me from purely theoretical considerations that injection of leukocytes intramuscularly in cases of neutropenia might furnish such products of disintegration, containing large amount of nucleic acid salts in a form probably well tolerated and active. At first (1930 to the early part of 1932) the leukocytes were separated in very simple fashion. Citrated blood in large tubes was centrifuged for 15 to 20 minutes at high speed. The grayish layer thus formed between the supernatant plasma and the packed red cells was then skimmed off with a pipette, along with some of the plasma and some of the red cells, and injected intramuscularly. Because of the imperfect method of preparation the doses used in the first 3 cases (Cases 8, 9, 10 of this series) contained approximately  $\frac{1}{2}$  the number of leukocytes used in Cases 1 to 7, inclusive. As a matter of fact the first patient treated received first small doses of whole citrated blood, with little effect and much local discomfort.

CASE 8.—G. V., a girl aged 13, had a chronic form of agranulocytosis with recurrent exacerbations. It is of interest to note that a lowering of the total leukocyte count occurred either during or a few days after the beginning of the menstrual flow. This phenomenon was also observed in Case 5 (Mrs. W. F. H.) by Dr. Klein and Dr. Neff and by Dr. Ellis in Case 6.

The relationship between menstrual period and acute attacks of agranulocytosis is of great interest, in view of the well known fact that the majority of cases of agranulocytosis occur in young and adult females. During one of these attacks, characterized by great prostration, ulcerations of the mouth, subfebrile temperature and bleeding from the nose, the patient received in 5 consecutive days intramuscular injections of leukocytic cream. Before treatment the leukocyte count was 1200 with 96 mature granulocyte per c.mm. After the 4th injection the total leukocyte count was 3350 with 435 mature granulocytes. Two days after the 5th injection the total leukocyte count was 4200 with 840 granulocytic cells and on the same day a new series of 5 daily injections was begun. After the 3d injection the total leukocyte count rose to 5700 with 3135 granulocytic cells. The ulcerations of the mouth at this point had healed and the temperature had returned to normal. Three days after the last injection, or 16 days after the first injection, the total leukocyte count was 6500 with 3315 granulocytes. Recovery or temporary improvement from previous acute attacks in this case, even less severe than the one here described, had always been much slower, the period being about 6 weeks or more for the improvement to manifest itself. The patient died recently of acute appendicitis.

CASE 9.—A. M., the second patient treated, a white male, aged 51, was first seen by me 1 week after the onset of symptoms, when he had a septic temperature, with daily elevations to 102° to 103° F., a diffuse ulcerative stomatitis with considerable swelling of the cervical lymph nodes, profuse bloody diarrhea and great prostration. The total leukocyte count was 950 with no granulocytes. The count was repeated on the same day, the result being 870 total leukocyte count without any granulocytes being



seen in several slides. This patient received daily doses of leukocytic cream for 6 days. After the 4th dose the total leukocytic count was 2900 with 335 granulocytes. Next day the temperature returned to normal and the mouth ulcerations began to heal rapidly. Diarrhea with bloody stools however, continued and a second series of 5 daily injections was begun, 3 days after the last dose of the first series. After the 3d injection the diarrhea practically disappeared, the stools no longer contained blood and the total leukocyte count was 4700 with 1645 granulocytic cells. Two days after the last injection of the second series, or 14 days after the treatment was begun, the total leukocyte count was 6300 with 3786 granulocytes, and no clinical manifestations of the disease. This patient had no recurrence, and died recently of carcinoma of the colon.

CASE 10.—C. Q., a white woman aged 72, had suffered for years from hypertension and failing cardiac action. She complained of great weakness for about 15 days before the onset of the severe symptoms which included deep ulcerations of both tonsils, fetid breath, superficial ulcerations of the gums, with small hemorrhages and moderate swelling of the cervical lymph nodes. The temperature was septic with elevation up to 104° F. on the 2d day. That day the total leukocyte count was 1450 with 44 granulocytic cells per c.mm. On the 3d day from the onset of fever, the leukocytic cream injections were begun, the patient receiving daily injections for 7 days. After the 3d injection the total leukocyte count was 1680 with 201 granulocytic cells. Clinical improvement began the same day with progressive healing of throat ulcerations. Next day the temperature returned to normal. After the 5th dose the total leukocyte count was 2450 with 808 granulocytic cells, and 3 days after the last dose the leukocytic count was 5600 with 3416 granulocytic cells. A few days later, while convalescing, the patient developed signs of acute phlebitis of the right leg accompanied by a temperature elevation to 101.5° F. It is of great interest to note that the leukocytes at this point rose to 12,500 with 23 per cent young forms (rod-nuclears and metamycocytes); that is, the patient had an adequate bone-marrow response to infection. A blood culture taken at this time yielded no growth and patient slowly made complete recovery. The patient has had no new attacks and is at present living and well.

In the early part of 1932 in connection with work on phagocytosis at the University of Pennsylvania, I devised a method of separation of leukocytic cream from the blood as follows:

**Method.** Withdraw the blood from the vein of the donor into citrate solution not less than 150 cc. Divide the blood in large tubes and centrifuge at high speed for 30 minutes. Carefully withdraw the clear supernatant plasma, part of which is kept for the preparation of leukocytic emulsion later. With a large mouth pipette and a rubber bulb remove carefully the buffy layer of leukocytes which has formed on the surface of the packed red cells. Do that for each tube and transfer the material to a Babcock cream tube. Add to this enough of the packed red cells to bring up well in the neck the surface of the fluid. Centrifuge again for 20 minutes at high speed. The leukocytes will now rise to the top. There are usually three well defined layers: (1) clear plasma; (2) suspension of leukocytes and platelets; (3) leukocytes mixed with some red cells. This last layer has been found to be richer in polys, while the topmost layer contains more lymphocytes. Draw off with a large-mouth capillary pipette this material, removing also the top layer of the packed erythrocytes. Suspend this material with plasma so as to make for each 100 cc. of blood used 5 to 10 cc. of suspension. The material is used intramuscularly. As a rule, with high speed of the centrifuge the volume of the packed leukocytes is 1.6 per cent of the amount of blood used,

and the suspension contains about  $\frac{2}{3}$  of the leukocytes present in the blood used. In smears of the suspension, the leukocytes appear very well preserved. It is desirable to check with a smear, or better, a cell count, that the suspension prepared is adequately rich in leukocytes. It is essential to separate the leukocytes from the blood as early as possible after the withdrawal of the blood from the donor. If for some reason the blood must be kept overnight, twice the amount of citrate should be used. The leukocytes thus prepared remain well preserved for a period of 7 days at least, although I have never used them after 5. Of course strict aseptic technique

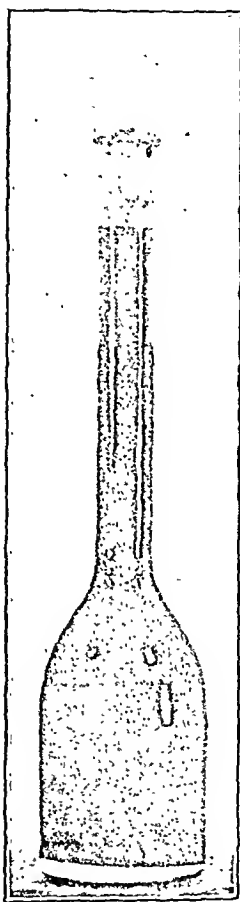


FIG. 1.—A Babcock cream bottle, showing from top to bottom small layer of plasma (dark), leukocytic cream (light) and packed erythrocytes.

must be employed. Another important point is to remove as much of the plasma as possible after the first centrifugation and to have the topmost layer of the material transferred in the Babcock cream bottle as high as possible in the neck. If for some reason (deficiency of red cells) this is not possible, the surface of the fluid may be brought to the proper point by introducing in the Babcock cream bottle sterile glass beads. If the material necessary is ready at hand the whole procedure for 500 cc. of blood can easily be accomplished in 2 hours or a little less.

The citrate solution, as anticoagulant, is prepared by dissolving 20 gm. of sodium citrate in enough sodium chlorid solution to make 100 cc. The

sodium chlorid solution percentage is 0.85. This solution contains for each cc. 200 mg. of sodium citrate, which is sufficient to prevent coagulation of 50 cc. of blood.

For all of the cases from 1 to 7 inclusive, each dose of leukocytic cream was prepared from 100 to 150 cc. of blood, unless otherwise stated. The intramuscular injection of this preparation has never given rise to reaction, neither local nor general, save slight local pain, even when repeated for a long period of time.

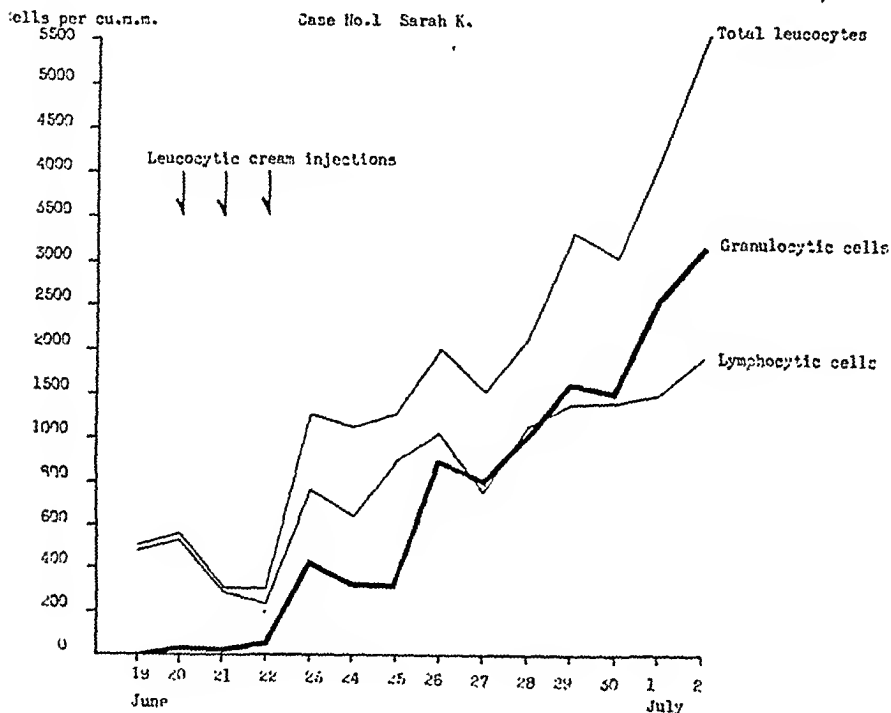


CHART I.

CASE 1.—S. K., a white, married woman aged 52, was admitted to the Bryn Mawr Hospital on June 18, 1932, on the service of Dr. H. W. Taylor with complaint of sore throat and weakness. The patient, 2 weeks prior to admission, had generalized body aching, followed by sore throat and subfebrile elevation of temperature. The patient did not recall any previous attacks of similar nature. On admission she appeared acutely and severely ill with profound prostration, stomatitis and pharyngitis, and temperature of 103° F. The blood examination on admission gave the following results: Hemoglobin, 11.84 gm.; erythrocytes, 3,040,000; leukocytes, 550; platelets, 354,000. The differential count showed: metamyelocytes, 1 per cent; rod-nuclears, 2 per cent; lymphoblasts, 2 per cent; prolymphocytes, 10 per cent; lymphocytes, 83 per cent; monocytes, 1 per cent; Tuerck cells, 1 per cent. The total content of granulocytic cells per c.mm. of blood (young cells only were seen) was therefore 15. Successive blood examinations and the dates of leukocytic cream injections are given on Chart I. A few purpuric spots appeared on her extremities shortly after admission, and on June 21 a pustular eruption developed around the anus.

For several days she was profoundly drowsy. Definite clinical improvement began about June 28, when the temperature returned to normal and remained so except for a slight subfebrile elevation later, during the course of a small abscess of the right foot accompanied by mild cellulitis of the leg. The patient was discharged in good condition on July 23 with a leukocyte count of 7400 and the following differential: rod-nuclears, 3 per cent; neutrophilic polys, 73 per cent; lymphocytes, 20 per cent; monocytes, 4 per cent. On August 19, 1932, there was a new mild attack of neutropenia with a leukocyte count of 3200 and 1236 granulocytic cells per c.mm. This attack was not accompanied by clinical symptoms and the patient quickly recovered without treatment. The patient is at present (June, 1933) living and well.

In addition to 3 injections of leukocytic cream the patient received 3 blood transfusions on June 21, 23 and 25, citrated blood being used in the following doses: 450 cc., 300 cc. and 550 cc. Pentose nucleotides injections were also used intramuscularly in daily doses from June 24 to June 30. It is seen, however, from Chart I that a sharp increase of the granulocytic cells of the blood occurred within 48 hours of the first injection of leukocytic cream, and that fully 24 hours before the first dose of pentose nucleotides was given the granulocytic cells had increased to 415 per c.mm. and the total leukocytes to 1250. If, in addition, one considers the fact that with pentose nucleotides a rise in the leukocyte count usually appears in the 5th day after the first dose, we may safely say that pentose nucleotides did not have anything to do with the sharp and early rise of the granulocytes which occurred after the injection of leukocytic cream and transfusions. It is possible that the later increase in leukocytes which occurred on the 28th and following days might have been at least partly due to the pentose nucleotides therapy.

CASE 2.—A. McC., a white, single woman, aged 36, was admitted to the Bryn Mawr Hospital on October 14, 1932; under the care of Dr. J. J. Sweeney and myself with complaint of sore throat, swelling of the face and neck, fever and severe general malaise. Two weeks prior to admission patient had suddenly developed swelling of the face and neck accompanied by sore throat with great prostration and febrile rise in temperature. The patient did not recall any similar attack. On admission the patient was gravely and acutely ill with intense drowsiness, swelling of the face and neck, severe diffuse stomatitis and pharyngitis with superficial ulcerations, covered with fibrinous exudate. The temperature was 102. The blood count gave the following results: hemoglobin, 14.55 gm.; erythrocytes, 3,900,000; leukocytes, 1100; platelets, 437,000, and the differential showed metamyelocytes, 0.5 per cent; rod-nuclears, 10 per cent; polys, 31.5 per cent; lymphocytes, 33.5 per cent; monocytes, 16 per cent; eosinophils, 0.5 per cent; basophils, 1.5 per cent; hemohistioblasts, 0.5 per cent; prolymphocytes, 5.5 per cent; monoblasts, 0.5 per cent. The granulocytic cells, 462 per c.mm., represented approximately  $\frac{1}{10}$  of the normal content. On October 15, 50 cc. of whole blood were given intramuscularly. On the 17th the first dose of leukocytic cream was given. This was followed next day by a return of the temperature to normal, a distinct clinical improvement and a sharp increase of the granulocytes in the blood. The clinical improvement with rapid healing of the mouth and throat continued uninterruptedly, the patient being discharged on October 26 in good condition and with the following blood picture: leukocytes, 3900; myelocytes, 1 per cent; metamyelocytes, 2 per cent; rod-nuclears, 15 per cent; polys, 54 per cent; prolymphocytes, 3 per cent; lymphocytes, 11 per cent; monocytes, 12 per cent; eosinophils, 1 per cent; Rieder cells, 1 per cent; the total number of granulocytic cells per c.mm. being therefore 2847.

Following the patient's discharge from the hospital, the blood picture

improved steadily until on December 29 it had returned to within normal limits. In this case no other therapeutic measure was employed except the 1 injection of whole blood and the 6 successive injections of leukocytic cream. The patient was followed with weekly and later fortnightly blood examinations. For 6 months the blood count remained practically normal except for a slight increase of the young granulocytes (rod-nuclears 7 to 8 per cent). On May 5, 1933, the total leukocyte count dropped to 4400 with 3212 granulocytic cells per c.mm. of blood. On May 20 the total leukocyte count was 3700 with 2775 granulocytic cells. The patient at this time complained of increasing although not severe weakness. On the 24th of the same month leukocytic cream injections were given for 5 consecutive days. Two days after the 1st injection the total leukocyte count had risen to 5300 and the total number of granulocytic cells to 3710, the patient feeling distinctly stronger. On May 29, the day after the last injection, the total leukocyte count was 5250 with 3517 granulocytic cells per c.mm. of blood. This case is still under observation.

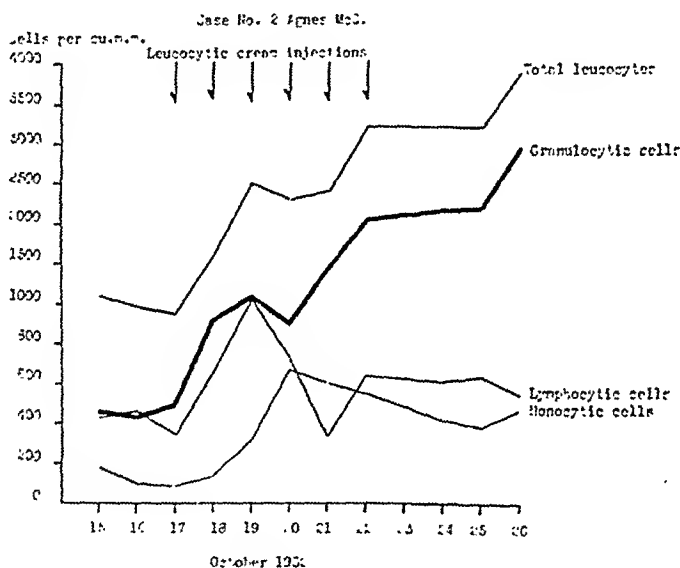


CHART II.

CASE 3.—G. B.; a white male, aged 41, was admitted to the Bryn Mawr Hospital on February 13, 1933, under the care of Dr. Klein and Dr. Taylor, with complaint of fever, weakness, and soreness of the mouth. On January 15, 1933, the patient had complained of moderate sore throat with severe joint pains and backache with a temperature elevation to 103° F. Sore throat and pains improved after 3 days of illness but for several more days the patient had an afternoon temperature rise to 100° to 102° with occasional night sweats. About January 8 a blood examination was done with the following result: hemoglobin, 14.5 gm.; erythrocytes, 4,340,000; leukocytes, 8800; neutrophilic polys, 34 per cent; lymphocytes, 61 per cent; monocytes, 3 per cent; eosinophils, 1 per cent; Tuerck cells, 1 per cent. Of the polymorphonuclear leukocytes 24 per cent were young forms. He returned to his business on January 24 feeling much better but still having a daily temperature elevation to 99° to 99.3°, in the afternoon. On February 11 he noticed soreness of the gums, and on February 12, had a temperature elevation to 103° with generalized pains and weakness. The leukocyte count at this time was 4500. On admission the temperature was normal

and there was a diffuse acute stomatitis with considerable redness and swelling of the gums. The blood count on admission showed leukocytes, 3900; metamyelocytes, 0.5 per cent; rod-nuclears, 1.8 per cent; polys, 0.5 per cent; prolymphocytes, 4 per cent; lymphocytes, 85.4 per cent; monocytes, 6 per cent; eosinophils, 1.3 per cent; Rieder cells, 0.5 per cent. There were numerous shadow cells and the total content of granulocytic cells was 160 per c.mm. The successive blood examinations and the dates of injections of leukocytic cream are summarized on Chart III.

Following the first injection of leukocytic cream the lesion of the mouth very rapidly improved along with the increase of the granulocytic cells in the blood. At the time of discharge on February 22 the mouth had entirely healed and blood count showed leukocytes, 6200; rod-nuclears, 10 per cent; polys, 60 per cent; prolymphocytes, 3 per cent; lymphocytes, 18 per cent; monocytes, 6 per cent; eosinophils, 3 per cent. The total granulocytic cell content per c.mm. was 4526.

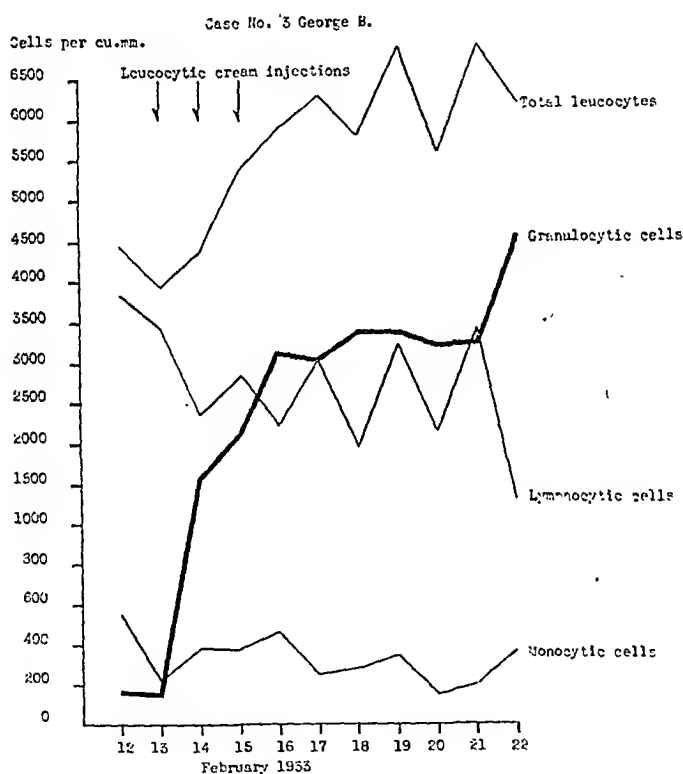


CHART III.

The patient has been under constant observation since discharge from the hospital and his health has remained good until present time and his blood picture normal except for a very slight lymphocytosis.

CASE 4.—Mrs. P. R., a white, married female, aged 34, was admitted to the Bryn Mawr Hospital April 11, under the care of Dr. H. C. Earnshaw, with complaint of severe sore throat, high fever and general malaise. On April 5 she had chill followed by very severe general prostration and headache. This continued next day but on the 7th she felt better. On April 9

she had a severe chill early in the morning followed by general malaise and severe sore throat. The temperature was then 104° F. and remained high with a septic curve up to the time of admission to the hospital. On April 10 the leukocytes were 3400 and the differential showed hemohistioblasts, 1 per cent; polymorphocytes, 7 per cent; lymphocytes, 59 per cent; monoblasts, 1 per cent; monocytes, 31 per cent; basophils, 1 per cent. No neutrophilic cells were seen on several smears.

On admission to the hospital at 10 A.M. the patient was very ill, with a temperature of 101°, a diffuse swelling of the face and neck on the left side, due to enlarged lymph nodes and severe tonsillitis. There were two grayish deep-seated ulcerations involving both tonsillar regions, covered by necrotic sloughs. Small ulcerations were scattered over the gums. The leukocytes were then 1400 per c.mm. and only 1 promyelocyte was

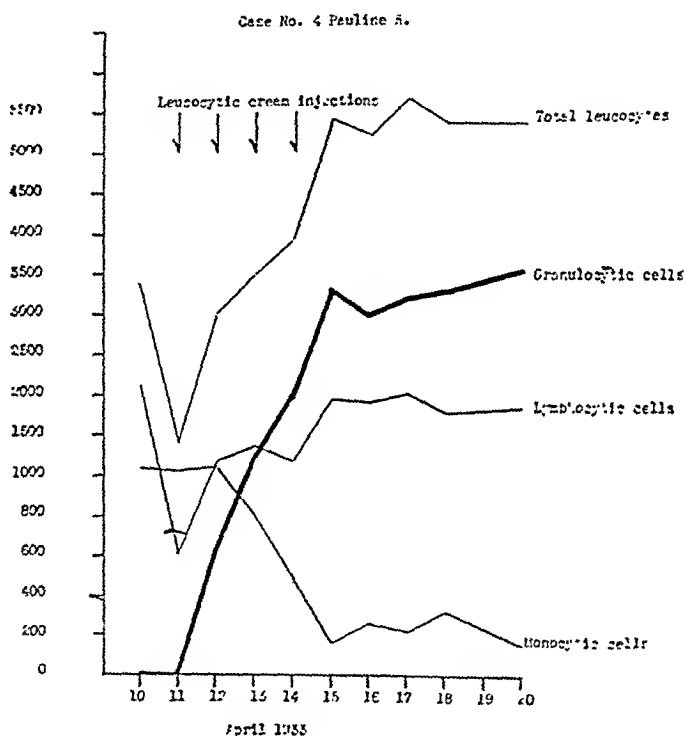


CHART IV.

seen in several smears. The first dose of leukocytic cream was given the same day at 5 P.M. and shortly after, a transfusion of 250 cc. of citrated blood was given, after which the patient had severe reaction with sharp rise in temperature. The next morning the patient felt much better and the temperature had returned to normal. The leukocyte count sharply increased to 3000 per c.mm. with a considerable shower of mature and young granulocytic cells. The throat lesion appeared in form of a white adherent membrane covering the whole uvula and both tonsillar regions. Although the mouth was still sore the patient felt much more comfortable. A second leukocytic cream injection was given to the patient April 12 at 10.30 A.M. and the clinical condition continued rapidly to improve along with the blood picture, the temperature returned to normal on April 12 on. Healing of the mouth lesion went on very rapidly. The temperature and the date of leukocytic cream injections are summarized in Chart IV.

The patient was discharged from the hospital on April 24 in excellent general condition, the mouth lesions entirely healed, and with the following blood picture: Hemoglobin, 14.9 gm.; erythrocytes, 4,220,000; leukocytes, 5300; rod-nuclears, 3 per cent; neutrophilic polys, 56 per cent; prolymphocytes, 4 per cent; lymphocytes, 31 per cent; monocytes, 2 per cent; eosinophils, 1 per cent; basophils, 3 per cent; or 3339 granulocytic cells per c.mm. of blood.

CASE 5.—Mrs. W. F. H., aged 47, was admitted to the Presbyterian Hospital on April 15, 1933, on the service of Dr. Thomas Klein, with chief complaint of soreness of gums with ulcerations, soreness of the tongue, pharyngitis with ulcerations, fever, weakness, and nervousness. Three weeks prior to this attack the leukocyte count was normal, although 3 or 4 days prior to this count the symptoms stated above had begun. The day before admission the leukocyte count was 1250 with 4 young polys and 96 lympho-

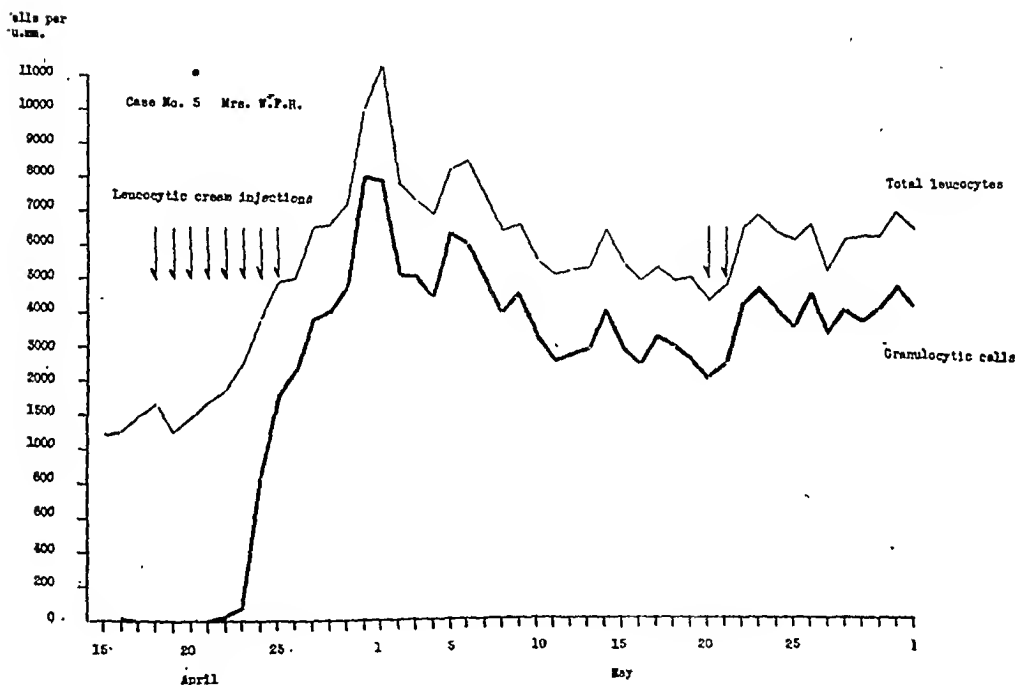


CHART V.

cytes. The history reveals that the patient had a similar attack 2 years before. She recovered from the first attack which was milder than the present, the therapy employed being sodium cacodylate hypodermically, and rest. After this illness the white cell count dropped at each menstruation to about 3000 with a percentage of polys of about 17. She recovered spontaneously from these attacks. For the past 6 months the count has been approximately normal.

This patient was operated upon in 1908 for hyperthyroidism and in 1930 had symptoms again, when she received light Roentgen ray therapy. This made conditions worse and she was operated upon again. In 1930 to help menopausal symptoms a light Roentgen ray dose was given. Shortly after this she had her first attack of neutropenia. It would appear that she is highly sensitive to Roentgen ray.

On admission on April 15, the temperature was 100° F., pulse 116, respira-



From Chart V it will be noted that the total leukocyte count after reaching a peak of 11,250 on May 1, with a total neutrophilic cell count of 7875 per c.mm., slowly dropped until on May 20 the total leukocyte count was 4300 with 2021 neutrophilic cells. The patient received 1 dose of leukocytic cream on May 20 and 1 on May 21. On May 22, that is, 2 days after the first dose, the total leukocytic count had risen to 6450 and the total number of neutrophilic cells to 4128, per c.mm. The patient's temperature had dropped to normal and remained normal thereafter, on the 24th of April, that is, 6 days after the first large dose of leukocytic cream was given. On April 28 she was out of bed and able to walk, the mouth had healed entirely and the patient felt altogether well. On May 8 the patient had returned to practically all normal activities of life and was discharged in good condition from the hospital on June 2. The point of great interest in this case as already noted is the coincidence of neutropenia with menstrual flow after the first severe attack.

Case 6.—Mrs. E. P. B., aged 30, was a robust white woman, who had attacks within the past 3 years. During the past winter attacks of sinus pains out of proportion to the sudden onset of the evening temperature elevation.

CASE 6.—Mrs. E. P. B., aged 30, was a robust white woman, who had returned to practically all normal after the coincidence of neutropenia with good condition from the hospital on June 2. The present illness had no febrile attacks within the past 3 years. During the past winter there had been repeated attacks of sinus pains out of proportion to the physical signs. The present illness had a sudden onset on the evening of March 25, with pains in the throat, ears and a temperature elevation to  $103^{\circ}$  F. There were mild ulcerations of the mouth, mostly peridental. The temperature subsided gradually until on March 28 it was  $100^{\circ}$  F., at which time a morphologic blood examination gave the following result (average of 2 determinations): total leukocytes, 2175; myelocytes, 0.5 per cent; young neutrophils (rod-nuclears and metamyelocytes), 14 per cent; neutrophilic polys, 6 per cent; lymphocytes, 65 per cent; basophils, 1 per cent; monocytes, 11.5 per cent; eosinophils, 2 per cent; agranulocytic angina was made, and cells per c.mm.). The diagnosis of agranulocytic angina was made, and blood transfusions were given on March 28, 29, and 30, totaling 1250 cc. A dose of pentose nucleotide was also given on March 30, but the reaction was so severe that it was not repeated. The behavior of the hematologic picture is summarized in Chart VI. The small peridental ulcerations healed and the patient seemed to be making a slow recovery, when a relapse occurred about April 25, 6 days after the menstrual period. The previous attack had also been shortly preceded by the menstrual period. The second attack was much more severe with extensive necrotic mouth ulcerations, bleeding from the gums, vomitus of blood with large pieces of gangrenous tissue, temperature elevation to  $105.3^{\circ}$  F. On April 27 the blood picture was total leukocytic count 2250, no granulocytic cells, lymphocytes 83 per cent, monocytes, 17 per cent. Blood transfusions totaling 2020 cc. were given each day from April 25 to April 30; the leukocytic cream injections were given each day from April 25 to April 30.

I am much indebted to Dr. Klein, Dr. Neff and Dr. Fowler for their kindness in furnishing material concerning this case.

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tions were begun also on April 26, and continued as illustrated in Chart VI, each dose of leukocytic cream corresponding to 150 cc. of blood. The rise of granulocytic cells began on the 28th, 2 days after the first dose of leukocytic cream and the first transfusion, when the total leukocytic count was 4000 with 120 granulocytic cells and continued rapidly until 5 days after beginning of treatment (April 30) the total leukocytes count was 5550, with 1276 granulocytic cells. The temperature steadily declined returning to normal shortly after, and massive sloughing of the mucosa of the mouth and upper digestive tract occurred.

On May 6 patient had another relapse but much milder, with no temperature elevation, and very superficial mouth ulcerations. It is important to note that this relapse was immediately preceded by a 2-day discontinuation of the leukocytic cream injections. Leukocytic cream injections were resumed, patient rapidly recovering from the second attack. The leukocytic cream injections were discontinued on May 24 for 4 consecutive days, this being immediately followed by another relapse with recurrence of

CELLS per cu mm

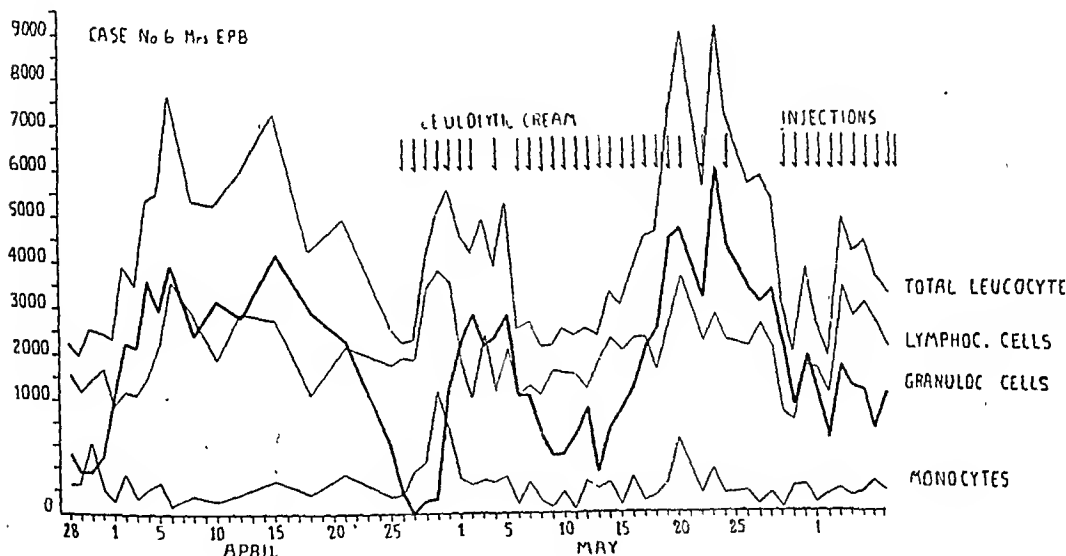


CHART VI.

infiltration and congestion of the gums far less severe than on previous occasions, and the elimination of a bone sequestrum left by the second severe attack. On June 3 the patient vomited a fairly good amount of fresh blood and on June 4, 5 and 6 there was vomitus with a small amount of chocolate blood. The leukocytic cream injections were resumed on May 29, and although the hematologic response was not as prompt as in previous occasions, the general condition as well as the mouth lesion improved greatly from June 3 on, she being generally much better than during any of the previous attacks. It is to be noted also that in the two relapses after the leukocytic cream was used, the total granulocytes did not go under 600 per c.mm. and that fever did not return. This third attack coincided with the menstrual flow, which began on May 24 and lasted for 5 days.\*

\* I am indebted for the notes on this case to Dr. Ellis, under whose care the patient has been, and to Dr. Belk, who furnished the laboratory data. She is still under treatment.

NOTE.—The count on June 12 on this patient after resumption of leukocytic cream injection gave the following results: Total leukocytic count, 5700; granulocytic cells per c.mm., 2451; lymphocytic cells per c.mm., 3192; monocytes per c.mm., 57.

CASE 7.—H. R., a man, aged 37, was admitted to the Jefferson Hospital on March 10, 1933, on the service of Dr. Harold Jones. At this time the patient complained of fatigue, pain over frontal sinuses, pallor and slight cardiac palpitation. His physical examination also showed severe visible pulsation in right side of neck and some enlargement of the submaxillary lymph glands. December 22, 1932, he had an attack of "grippe." He was forced to get out of bed because of illness of his wife but felt extremely weak. He returned to bed on the same day and remained there for 1 week. After this he felt better for awhile. On January 25, 1933, he consulted a physician, who remarked the pallor. Blood count showed red blood cells, 2,000,000. He was given liver and fresh vegetable diet, iron and arsenic, which treatment was continued until February 22, 1933, when a blood count showed no improvement. He was then referred to Dr. Jones and sent to the hospital. The patient had noticed slight shortness of breath on exertion and some cardiac palpitation for 2 months before admission. On admission to the hospital the temperature was 99° F. On March 19 and following days there were daily elevations up to 103.2° F. The temperature steadily but slowly decreased after March 25, returning to normal on April 8 and remaining so thereafter. Ulcerative lesions of the lips appeared on March 30, and a hard painful swelling of the rectum started on March 25, which on incision yielded small amount of bloody serum. This patient received 9 doses of pentose nucleotides from March 25 to March 30, 7 leukocytic cream injections were given from March 31 to April 7, and whole blood transfusions from 160 to 220 cc. on March 24, April 5, 10, 13, 17, 22, 26 and May 1, 3, 8, 12, 16, 20, 23 and 26. A sharp increase of the total leukocyte count occurred as follows: March 30, 1250; 31st, 2250; April 1, 5200; 3rd, 3100; 4th, 5200; 5th, 5900; 6th, 7600; 7th, 10,900. The differential count on April 1 showed a considerable increase of immature and mature granulocytic cells, but this did not continue, the bulk of the cells counted in successive days being erythroblasts, basophilic and eosinophilic. The clinical condition, however, greatly improved, and the rectal lesion spontaneously resolved and ruptured, healing completely. The patient is at present out of the hospital, still showing a severe neutropenia. The complexity of the case and the multiplicity of therapeutic measures employed do not allow any conclusion as to the effect that the injections of leukocytic cream may have had on the course.

Summarizing the effect of the leukocytic cream injections in 10 cases of agranulocytosis, I may state that in Case 1 an acute case, severe both clinically and hematologically, a sharp increase of granulocytes occurred within 48 hours of the first injection of leukocytic cream and continued thereafter, although only 3 injections were given. In Case 2, an acute case clinically severe but hematologically showing less severe neutropenia, the increase of the granulocytes occurred 24 hours after the first injection of leukocytic cream, and the hematologic and clinical improvement proceeded rapidly and uninterruptedly thereafter. This patient, 6 months after the first attack, had a mild hematologic relapse which again responded within 48 hours to the leukocytic cream injection. In Case 3, acute, clinically of moderate severity but with severe neutropenia, the increase in the granulocytic cells occurred within 36 hours, with a rapid and continuous improvement thereafter. In Case 4, acute, very severe granulocytes in the circulating blood occurred within 24 hours of the first injection of leukocytic cream along with clinical improvement,

the patient's condition as well as the hematologic picture improving continuously and rapidly thereafter until complete recovery. In Case 5, in a second attack of great severity both clinically and hematologically, the hematologic and clinical response to the leukocytic cream injections occurred 3 to 4 days after the first injection and continued thereafter rapidly and continuously along with the clinical improvement. A mild hematologic relapse during the convalescence, without clinical symptoms, responded within 48 hours from the first of two leukocytic cream injections. In Case 6, an extremely severe case both hematologically and clinically, of the acute recurrent type, as long as leukocytic cream injections were kept up the hematologic picture remained fair and the patient free from symptoms, but discontinuance of the leukocytic cream injections was followed by relapse, far less severe however than those previous to the leukocytic cream injections. This patient is as yet under treatment and will be fully reported by Dr. Ellis. In Case 7, one of great severity both clinically and hematologically, the effect of leukocytic cream injections was doubtful. Case 8, one of chronic type with recurrent exacerbations, was treated with somewhat smaller doses of leukocytic cream but responded nevertheless within 3 days with a sharp increase of the granulocytic cells, the hematologic and clinical improvement continuing thereafter without interruption. In Case 9, a case of acute primary attack, severe both clinically and hematologically, hematologic and clinical improvement occurred within 3 days of the first dose of leukocytic cream and continued thereafter until complete recovery. Case 10, an acute primary attack, clinically and hematologically fairly severe, responded clinically and hematologically to the injections of leukocytic cream within 48 hours of the first dose with improvement progressing steadily thereafter to recovery.

In Case 1 pentose nucleotide injections were given when response to the leukocytic cream injection was already fully established. Case 2 received no other treatment except the leukocytic cream injections. Cases 3, 8, 9 and 10 likewise received nothing but leukocytic cream injections. Case 4 received leukocytic cream injection with a single small transfusion. Case 5 received leukocytic cream injections and hypodermic injections of sodium cacodylate. Case 6 received transfusions at the beginning of the treatment along with leukocytic cream, thereafter leukocytic cream only. Case 7, as stated in the history of the case, received leukocytic cream, transfusions and pentose nucleotides. It appears, therefore, that in agranulocytosis, both in single acute attacks or in recurrence, the leukocytic cream injections were followed by an increase of circulating granulocytic cells along with marked clinical improvement, in 9 out of 10 cases in which it was used. The clinical response and the hematologic improvement have been on the whole strikingly parallel and have progressed continuously after they have begun. The response occurred as a rule from 1 to 3 days after the first dose.

In all of the cases thus treated the hematologic response was characterized by an early shower of young granulocytes and later progressive increase of the mature polymorphonuclears.

In any work claiming results for new therapeutic measures it is of course of prime importance to furnish adequate controls. This is in all cases very difficult and particularly difficult with a relatively uncommon disease, such as agranulocytosis. Naturally all the cases that have recently come to my observation have been treated with leukocytic cream injections. In view of the known high mortality in this disease one is not justified in withholding any treatment that offers promise of being beneficial. In the records of the Bryn Mawr Hospital from 1928 up to the present, in addition to the cases already reported, there is only one ascertained case of agranulocytosis. This was a woman, Mrs. M. B., aged 27, who on January 1, 1929, had an attack of grippe. About a month later the patient had an attack of sore throat with fever and malaise. On February 8 she was admitted under the care of Dr. Council and Dr. Ellis. This time she had severe ulcerations of the throat, febrile irregular temperature and a severe neutropenia with granulocytic cells as low as 100 per c.mm. of blood and the total leukocytic count considerably below 1000. During this first attack the patient received 12 blood transfusions, totaling 2160 cc., 7 Roentgen ray treatments and liver extract. Patient was readmitted to the hospital on June 25, 1929, with a severe relapse. During this relapse the temperature was constantly above 103°, reaching 106° on one occasion, the total leukocyte count was always below 900, being as low as 200, and no polymorphonuclears were seen in any of the numerous smears examined. The patient had severe peridental necrosis, developed signs of pneumonia, and died July 3. During the second attack she had received 5 doses of Roentgen ray and 11 blood transfusions, totaling 2700 cc. (This case also will be reported in detail by Dr. Ellis.)

Other cases that I have had occasion to see have been variously reported. In addition to the statistical data of Doan, previously referred to, Fitz-Hugh and Comroe<sup>11</sup> have reported 18 well studied cases, 15 of which died. Dameshek and Ingall<sup>10</sup> reported 9 cases of agranulocytosis of which 7 died. Considering the fact that agranulocytosis is not a disease entity and that practically no 2 cases run exactly alike, it becomes absolutely impossible to control properly the therapeutic effect of any material. Inasmuch as the purpose of this paper is merely to present facts concerning the action of leukocytic cream injections, and the method for the preparation of this leukocytic cream rather than claim specific or non-specific virtues for it in the treatment of agranulocytosis, the lack of an adequate control series is of less moment. What these patients would have done without the injections of leukocytic cream is purely a matter of speculation. Unquestionably some of the milder cases would have recovered spontaneously; the spontaneous

recoveries are as a rule, however, slower than those described here. On the other hand, extremely acute fulminating cases are probably not helped by any therapeutic measure.

In addition to the cases of agranulocytosis, leukocytic cream injections have been used in a small number of other forms of neutropenia. Three of these miscellaneous cases are presented here.

**Miscellaneous Cases Treated with Leukocytic Cream.** CASE A.—Miss M. B., aged 14, a case of acute lymphoblastic leukemia, admitted to the Bryn Mawr Hospital on May 2, 1933, on the service of Dr. Harvey, showed a constant neutropenia and was treated with 4 separate series of leukocytic cream injections. Accompanying table shows that each one of these series of injections was followed by a sharp increase in the number of circulating granulocytes. The number of these cells also very sharply dropped, usually within 48 hours of the last injection. This case will be

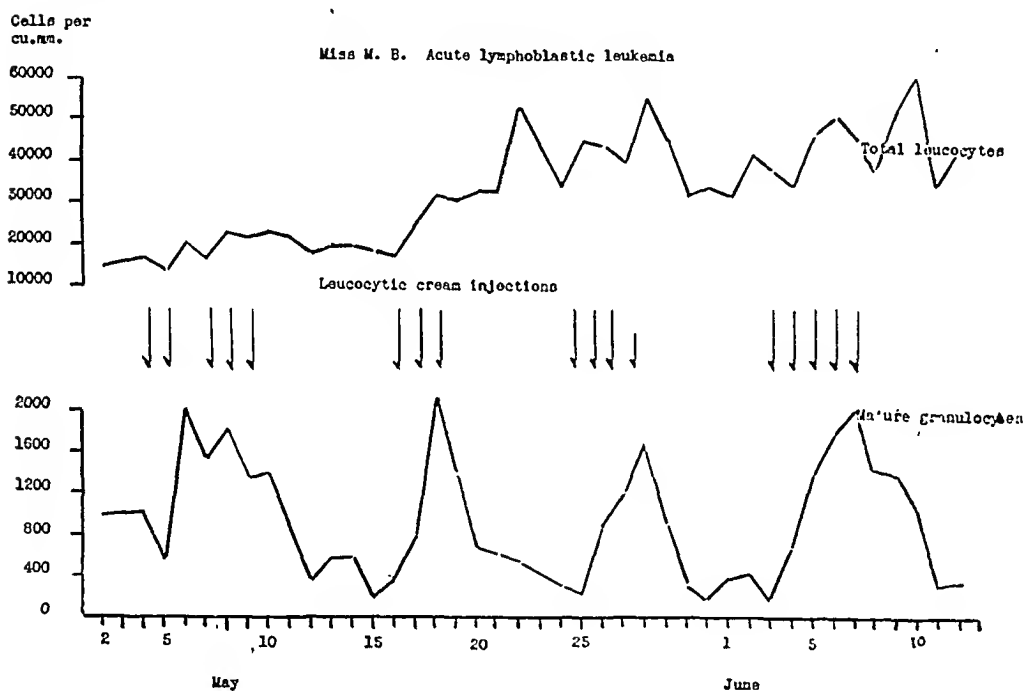


CHART VII.

reported in detail later, but it is interesting to notice that the patient has been free so far from the mouth infection so common in this disease, and that superficial ulcerations of the mouth and slight oozing of blood which occurred on June 1 rapidly disappeared when following leukocytic cream injections the granulocytic cells in the circulating blood increased from less than 200 to over 2000 per c.mm. in a few days.

CASE B.—Mrs. M. H., was admitted to the Bryn Mawr Hospital May 8, 1933, under the service of Dr. Harvey and later transferred to the service of Dr. Billings, with a diagnosis of bleeding carcinoma of the transverse colon, which was later confirmed by operation and tissue examination. The blood picture of this patient was carefully followed for 4 days prior to the leukocytic cream injections. For the 4 days preceding the first inoculation of leukocytic cream the average of the total leukocyte count was 3562 and the total granulocytic count 2365 per c.mm. with small daily variations.

Two doses of leukocytic cream were given on May 12 and 13. On May 13, within 24 hours of the first injections, the total leukocyte count was 4800 and the number of granulocytic cells 3792. This improvement continued for 3 days, thereafter slightly and slowly decreasing.

CASE C.—Baby A. S., aged 23 months, male, was admitted to the Bryn Mawr Hospital on May 31 on the service of Dr. Longaker with diagnosis of acute bilateral mastoiditis, for which he was operated upon. The child had septic temperature with rise to 105.5° F. Two blood cultures showed *S. hemolyticus* in very large number, the child later developing extensive cellulitis of the arm and leg. On June 3 patient had a leukocyte count of 7100 of which only 1633 cells were mature polys. The baby received 5 leukocytic cream injections. Within 24 hours from the first injection the blood examination showed a total leukocyte count of 9500 with 3800 mature polys; 4 days after the first injection the total leukocyte count was 15,000 with 5250 mature neutrophils. In view of the fact that in cases of this sort the fluctuation of the total cell count as well as of the mature neutrophils is often great, it is not possible to state what effect the leukocytic cream injection had, inasmuch as only the examination of numerous cases might decide the question. In this case the hematologic improvement was paralleled by a slight but definite clinical improvement.

Leukocytic cream injections in adequate amounts have been so far tried in 3 normal patients carefully studied. None of them appeared to show any increase of granulocytes or an increase of the young forms above what might be considered the physiologic fluctuations.

It is too early to attempt to form a theory in regard to the mechanism of the action of leukocytic cream injections, if any. I venture, however, to say that because of the short interval of time between the injections and the hematologic response in all probability we are dealing with a phenomenon of maturation more than multiplication of cells. It is also possible that the release of already mature cells is affected, although this seems to be less likely.

**Conclusions.** Evidence is presented that injections of leukocytic cream intramuscularly in severe neutropenias is followed in most cases within 1 to 4 days, usually 48 hours, by an increase of mature granulocytic cells in circulation, along with a considerable clinical improvement.

A method for preparation of the leukocytic cream is given.

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## THE EFFECT OF HYPERPYREXIA INDUCED BY RADIATION UPON THE LEUKOCYTE COUNT.

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VARIOUS methods are now available which permit controlled elevation of the temperature of the human body by means of physical energy. This affords opportunity of studying the physiologic changes occurring in the body as a result of such temperature elevation apart from infections. In fever produced endogenously by invading microorganisms, or the injection of foreign proteins or toxic substances, it is not possible to separate the thermal from the other factors. We observed changes occurring in the leukocyte count during hyperpyrexia produced in the human subject as a result of exposure to radiations of a wave length of about 30 m. In most instances the temperature as determined by rectal thermometer was raised to 104° to 106° F. and maintained for 3 to 4 hours by surrounding the patient with a hood containing some carbon filament lamps.

Our study included 39 determinations in 24 cases, suffering from the following diseases: chronic arthritis, 6 cases; gonorrheal arthritis, 3; central nervous system lues, 5; multiple sclerosis, 2; and 1 case each of encephalitis, basal ganglion disease, pelvic inflammatory disease, sympathetic ophthalmia, sciatic scoliosis, and carcinoma of the stomach. On several occasions, counts were taken on the morning and sometimes on the afternoon of the following day. The blood was usually taken from the finger tip. Smears were stained with the Jenner-Giemsa and Wright solutions. Hemoglobin determinations were made by means of the Sahli technique. The varieties of the white blood cells were grouped into the staff neutrophils, the total neutrophils, the monocytes and lymphocytes.

**Results.** The initial reaction was a reduction in the number of white blood cells. This was usually seen at the end of the first or second hour after the beginning of the treatment. In 6 instances this initial diminution in the number of white blood cells was not observed. It is possible that the failure to make this observation was due to the fact that the first blood count following the start of the treatment was not made soon enough. In most instances the reduction in the number of white blood cells amounted to from 25 to 30 per cent (limits, 2 and 40 per cent).

By the 3d, 4th or 5th hour after the onset of treatment, the



number of white blood cells had risen to a level above the initial figure. The peak of the leukocyte count usually occurred at the 6th to the 9th hour. The increase in the number of the white blood cells averaged about 50 per cent in those instances where the count was followed for a period of about 6 to 8 hours. It averaged about 80 per cent where the count was followed to its highest point. At times this increase amounted to more than 100 per cent. In only 2 instances did we fail to observe an increase in the number of the white blood cells. The leukocyte count rose as high as 22,600. Immature forms such as myelocytes, metamyelocytes, premyelocytes, and myeloblasts were seen.

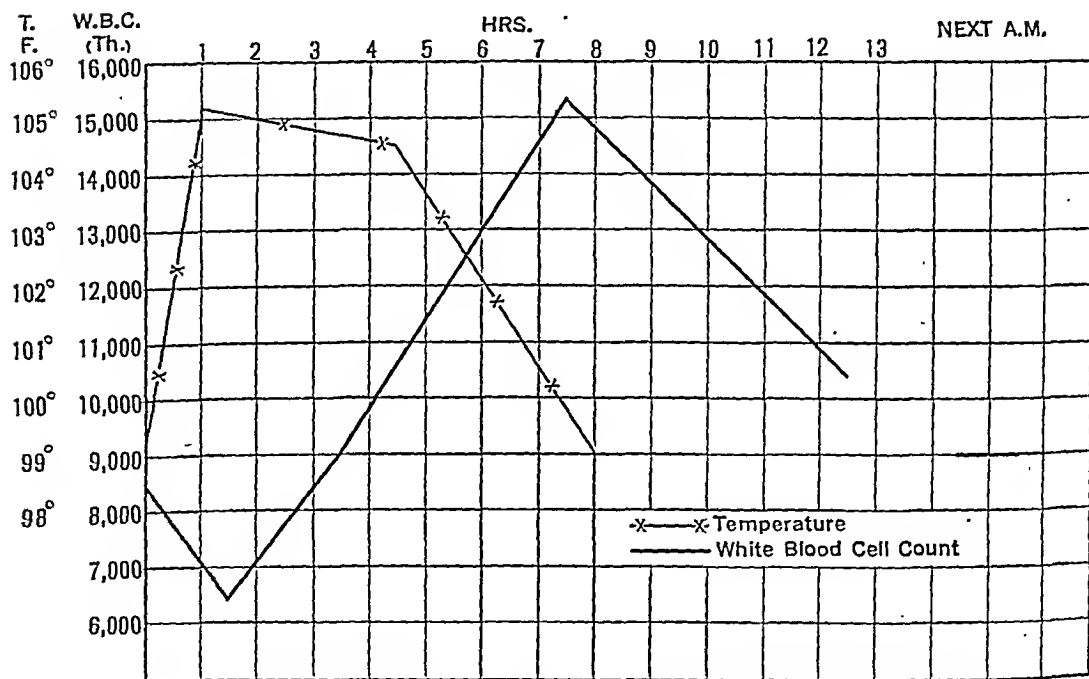


FIG. 1.—Composite graph showing relationship between temperature elevation and the leukocyte count.

The greatest percentage of increase was seen in the staff cell count. This increase averaged about 300 per cent and was about 200 to 300 per cent in most instances, on one occasion rising to 1420 per cent. The peak of the staff cell count usually occurred at about the 9th hour. In about  $\frac{1}{3}$  of the observations the rise in the number of staff cells was preceded by a fall, usually occurring at the end of the 1st or 2d hour, and which, in the majority of cases, amounted to about 30 per cent. The swing of the staff cell count coincided more or less with that of the total neutrophils.

The total number of the neutrophils showed an average diminution of about 25 per cent, occurring usually at the 1st, 2d or 3d hour.

If the count was followed long enough, the maximum rise was seen to occur from the 5th to the 9th hour. The average increase was about 140 per cent.

In about  $\frac{1}{2}$  of the instances there was a diminution in the number of monocytes, which averaged about 45 per cent. The low point of the fall usually occurred at the 1st, 2d or 3d hour; the high point, from the 5th to the 14th hour. The average percentage of increase was about 270.

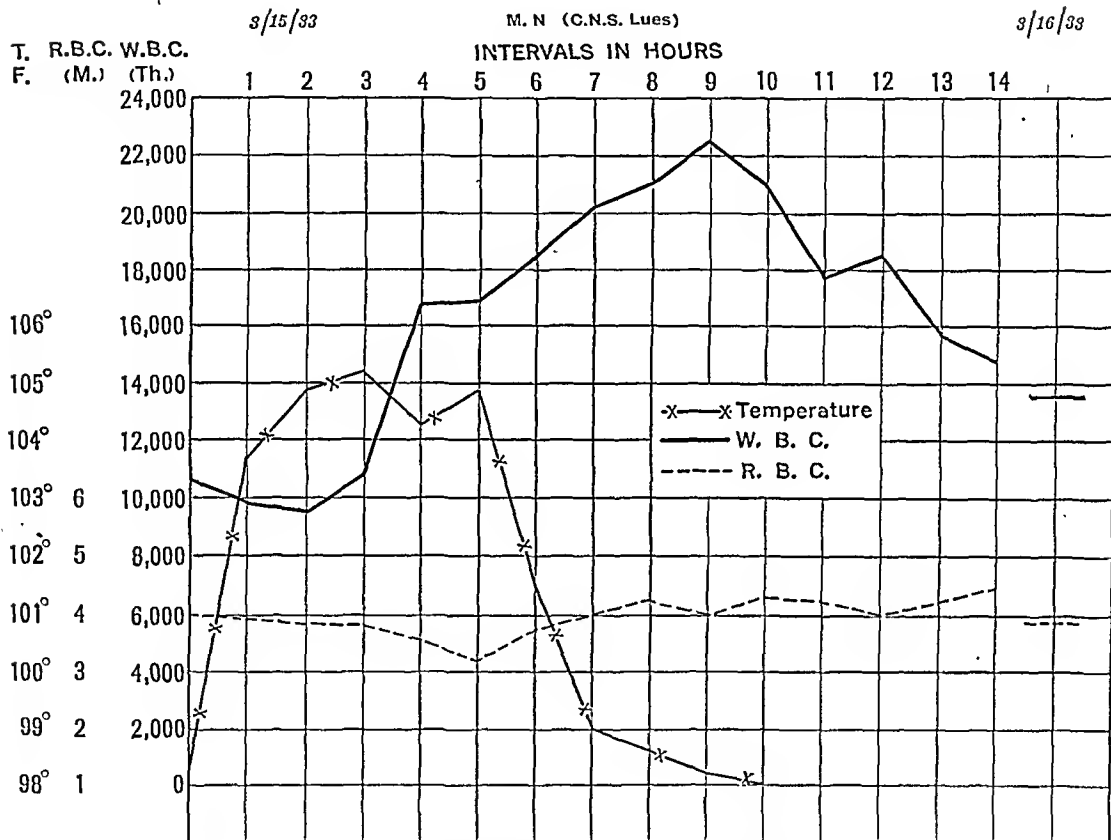


FIG. 2.—A case representing the relationship between systemic temperature, leukocyte and erythrocyte levels.

The average reduction in the number of lymphocytes amounted to about 40 per cent. The smallest numbers were observed at the 3d or 4th hour. In about  $\frac{1}{2}$  of the instances the lymphocyte count had not returned to its original figure when blood counts were made for a period of only 6 to 8 hours. In the other  $\frac{1}{2}$  the average rise was about 35 per cent. When the counts were observed for 13 to 14 hours, it was noticed that the time of the height of the rise occurred from the 6th to the 11th hour and the increase averaged about 90 per cent.

In general, the white blood cells from the bone marrow first showed the stimulating influence of the hyperpyrexia—the segmented neutrophils and the staff neutrophils. The monocytes, whose origin

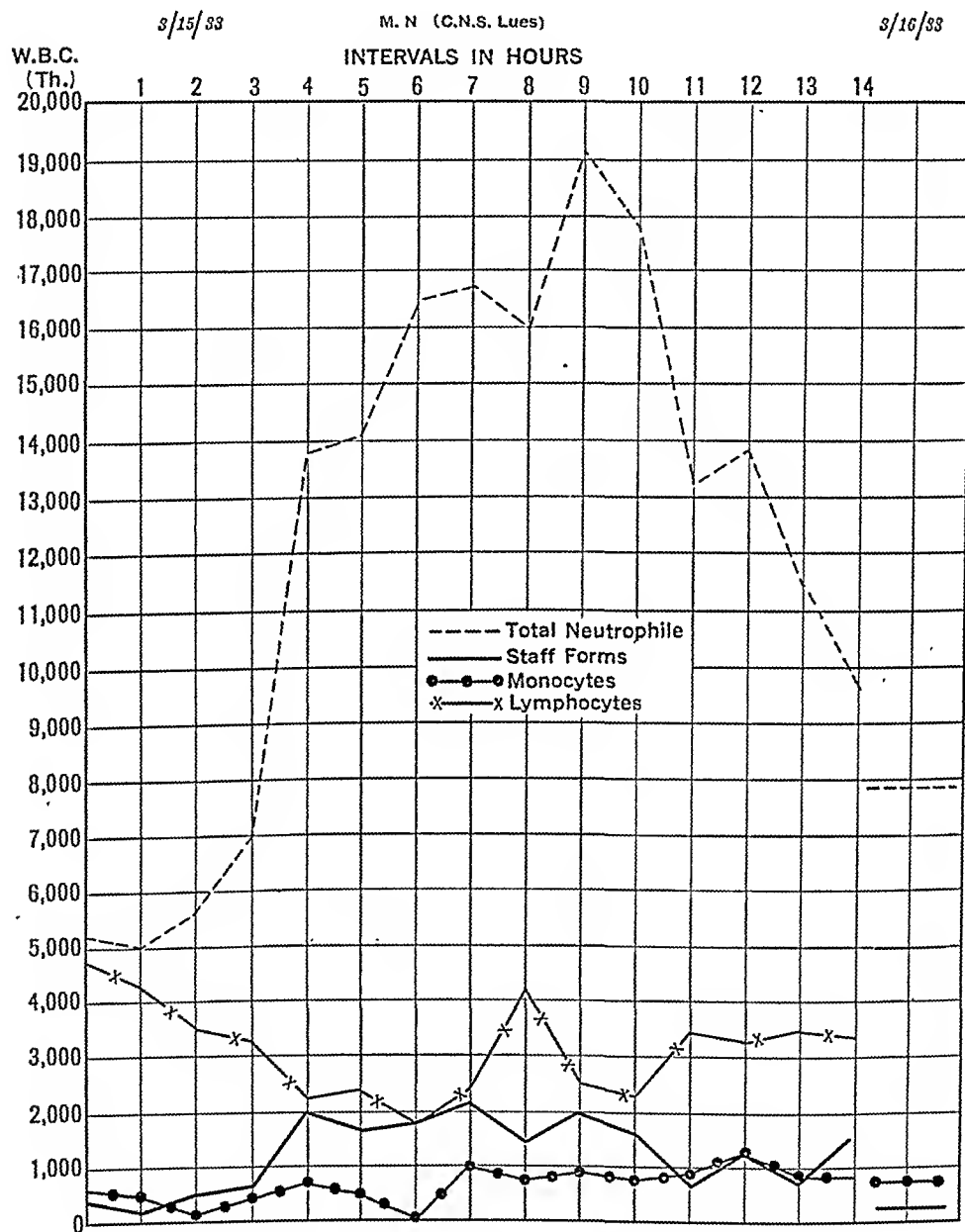


FIG. 3.—The differential count of the leukocyte response indicated in Fig. 2.

is ascribed to the reticuloendothelial system<sup>1</sup> are the next to give evidence of an increase in their number, and, last, those from the lymphatic system—the lymphocytes.

When the hyperpyrexia treatments were administered at frequent

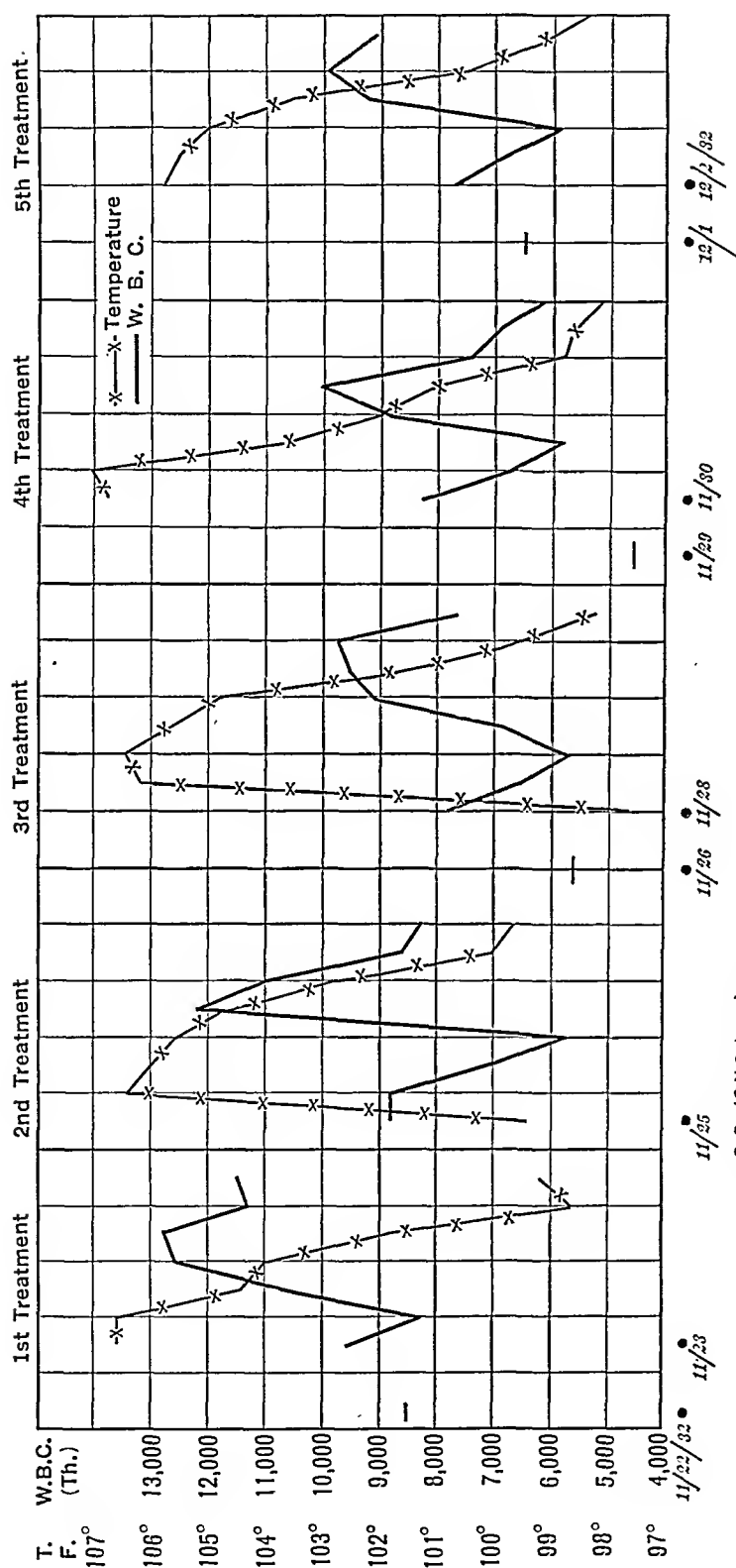


Fig. 4.—Effect of frequently repeated hyperpyrexia treatments upon the leukocyte count.

intervals, *e. g.*, every other day, the leukocytic response became diminished and the number of the white blood cells on the days between treatments became lower.

**Comments.** From these observations it will be noted that the characteristic change in the number of white blood cells occurring during electrically induced hyperpyrexia is an initial fall followed by a rise in the number of the leukocytes. This swing took place in nearly all of the cases studied. It occurs even when there has already been a retardation of the mechanism which is responsible for a diminished number of white blood cells in the peripheral circulation (as in a case of carcinoma of the stomach exposed to high-voltage Roentgen ray radiations and showing a severe leukopenia).

Three to 5 hours elapse before the stimulating influence of the hyperpyrexia upon the hematopoietic system becomes evident in the peripheral circulation, as determined by the enumeration of the white blood cells and the appearance of immature forms.

It should be of interest to the clinician to observe that the maximum leukocytosis may occur at a time when the temperature has returned to the normal level. This may explain the finding of an increased number of white blood cells in a patient who may have had an elevation of temperature a few hours preceding the taking of the count.

A leukocytosis occurs even though the temperature be only slightly elevated and maintained for a short period of time. The height of the leukocyte rise appears to depend not only upon the height to which the temperature is raised, but also upon the length of time during which the temperature elevation persists.

The change in the number of white blood cells cannot be explained on the basis of a change in the blood volume. The percentage of hemoglobin and the number of red blood cells does not show a fluctuation at all comparable to that occurring in the number of white blood cells. These patients may lose as much as 2 to 3 liters of fluid (mainly through the sweat). This may be balanced, however, by the fluid intake if the patient is permitted to drink all the fluid he desires. Also, the increase of immature cells could not be explained in this way.

Leukocytosis has been shown to occur after the injection of malarial plasmodia<sup>2</sup> and typhoid vaccine.<sup>3</sup> In both of these instances a marked elevation of body temperature occurs.

According to Mueller, the fall in the number of white blood cells occurring during the initial stage of temperature elevation can be explained on the basis of an overbalance of the sympathetic nerves. "The liver and the vessels of the splanchnic region show a contrary fixation when the parasympathetic vasodilating nerves prevail." The splanchnic region, as represented in one part by the liver, and the periphery, as represented in one part by the skin, form 2 large sys-

tems balancing each other as far as the nervous control is concerned and holding in balance also the number of leukocytes in their vessels."<sup>4</sup> While this may be a possible explanation for the initial changes observed during hyperpyrexia, we have no evidence indicating capillary contraction. Unlike the condition noted during the period of chill following intravenous injection of typhoid vaccine, the skin surface during the administration of electrically induced hyperpyrexia is warm, its temperature begins to rise, and sweating usually occurs within a few minutes.

The subsequent leukocytosis must be due to stimulation of the hematopoietic system as evidenced by the occurrence of immature forms such as myelocytes, metamyelocytes, premyelocytes, and myeloblasts. Jacobsen and Hosoi, in discussing the morphologic changes occurring in tissues as a result of the development of high temperature produced by means of the electric current, describe a congestion of the organs and evidence of the stimulation of the bone marrow.<sup>5</sup>

The changes in the number of white blood cells after typhoid vaccine injection and induced malaria have shown an initial diminution followed by a leukocytosis similar to ours. Leukocyte counts as high as 62,000 per cu.mm. have been reported after the injection of typhoid vaccine intravenously.<sup>7</sup> Our highest count has been 22,600.

Weiss<sup>2</sup> has described blood changes occurring during the paroxysm of malarial fever as consisting of a rise, first, in the number of neutrophils, followed by an increase in the number of monocytes and then by an increase in the number of lymphocytes. This corresponds to the changes we have observed. Schilling has described these as phases of struggle, defense or subjection, and healing.<sup>1</sup>

The diminution of the leukocytic response after repeated hyperpyrexia treatments with the lowering of the white blood cell count on the days between treatments would indicate a lessening of the hematopoietic system's reaction to the stimulating influence of heat. Similarly, it has been observed that after repeated intravenous injections of typhoid vaccine, the leukocytic reaction becomes less marked.<sup>7</sup> This diminution of the leukocytic response has also been noted to occur following the repeated administration of radiotherapy treatments for general paralysis.<sup>8</sup>

**Conclusions.** Hourly observations were made of the changes occurring in the leukocyte count of patients suffering from varied diseases in whom hyperpyrexia was induced by means of radio waves of 30-meter length.

An initial reduction, about 25 to 30 per cent, in the number of leukocytes regularly occurs, usually during the 1st or 2d hour of treatment. This is constantly followed by a leukocytosis whose maximum, amounting to about 80 per cent above the initial figure, occurs about the 6th to the 9th hour.

These variations are due mainly to changes in the total number of neutrophils, of which the staff neutrophils show the greatest increase. These changes, together with the appearance of other immature forms, indicate a stimulation of the bone marrow.

At a later stage the monocytes and lymphocytes also increase in number.

Repeated stimulation by heat is followed by a reduction in the leukocytic response.

I desire to express my thanks to Dr. Willys R. Whitney, of the General Electric Company, for placing a short-wave radiation machine at my disposal, and to Miss Janet Greenberg and Miss Rosalie Koplik for their technical assistance.

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### THE RELATIONSHIP BETWEEN THE ERYTHROCYTE SEDIMENTATION RATE AND THE FIBRINOGEN CONTENT OF PLASMA.

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DURING recent years the rate of erythrocyte sedimentation has been shown to be influenced by many factors. It has been demonstrated<sup>12,14</sup> that to obtain a reliable sedimentation-rate measurement, venous stasis should be avoided in collecting the blood, heparin should be used as the anticoagulant, the blood should not stand more than 3 hours before the test is started, and the room temperature should remain between 20° and 25° C. during the measurement. Further the rate of settling bears an inverse ratio to the volume percentage of red blood cells;<sup>\*4,5,12</sup> the fewer the red blood cells in a specimen of blood, the faster the sedimentation rate. In a previous

\* For the purpose of brevity, here and elsewhere in this note complete references are not given. The bibliographies of two reviews (References 4 and 8) are referred to repeatedly.

communication<sup>12</sup> a method was reported by means of which the sedimentation rate for any specimen of blood can be corrected to the rate which would have been obtained if the sample of blood had contained 45 volumes per cent of cells. The rate thus obtained was termed "the corrected sedimentation index." This method,<sup>12</sup> which embodies all the precautions enumerated by Rourke and Plass<sup>14</sup> and also corrects for variations in cell volume percentage of the blood, appears to us more suitable for further correlation of the erythrocyte sedimentation rate with accompanying chemical or physical changes in the blood plasma than other methods in clinical use.

Several investigators have reported varying degrees of correlation between increased fibrinogen content of the plasma and increased rate of erythrocyte sedimentation.<sup>2,3,4,6,7,10</sup> It has been observed, in addition, that when the fibrinogen content of the plasma is reduced by administering chloroform to the dog, the erythrocyte sedimentation rate is diminished in proportion to the decrease in plasma fibrinogen content.<sup>13</sup> In only one of the above mentioned studies<sup>2</sup> was the sedimentation rate corrected for variations in the cell volume percentage of the blood, and here a close correlation was observed between the corrected sedimentation index and the plasma fibrinogen content in patients with rheumatic fever.

Simultaneous measurements of the corrected sedimentation index and plasma fibrinogen content have been made in this laboratory in a large number of normal individuals and in patients with various pathologic conditions. It seemed desirable to assemble this data to determine the correlation between the plasma fibrinogen content and the corrected sedimentation index.

**Results and Discussion.** In Fig. 1 the fibrinogen content of the plasma, measured as fibrin by the method of Wu,<sup>16</sup> has been charted against the corrected sedimentation index in 190 instances. The diagnoses in the subjects on whom observations were made are presented in Table 1: 39 clinical conditions are represented. Not more than four points have been charted from measurements on any individual during the course of his disease. The normal area (Fig. 1) for fibrinogen content and corrected sedimentation index has been blocked out between the limits of 0.22 to 0.32 gm. per cent fibrinogen, and 0.08 to 0.35 mm. per minute corrected sedimentation index. These limits are based on observations made in this laboratory in a large series of normal individuals. The open dots at the extreme top of the chart represent sedimentation rates so rapid that the corrected sedimentation indices had to be interpolated above the upper line on the correction chart presented in the paper describing the method.<sup>12</sup> The manner in which this interpolation is made is described in the same communication. The crosses in Fig. 1 represent the results of 6 tests on 5 patients who had acute hepatitis at the time of the test or who had in the past been hospitalized for acute hepatitis.



The degree of correlation, shown graphically in Fig. 1, indicates a close relationship between the plasma fibrinogen content and the corrected sedimentation index. It has been established that the fibrinogen content of the plasma as well as the rate of erythrocyte sedimentation is increased in infectious diseases.<sup>8</sup> Plass and Matthew<sup>11</sup> demonstrated that the plasma fibrinogen content in-

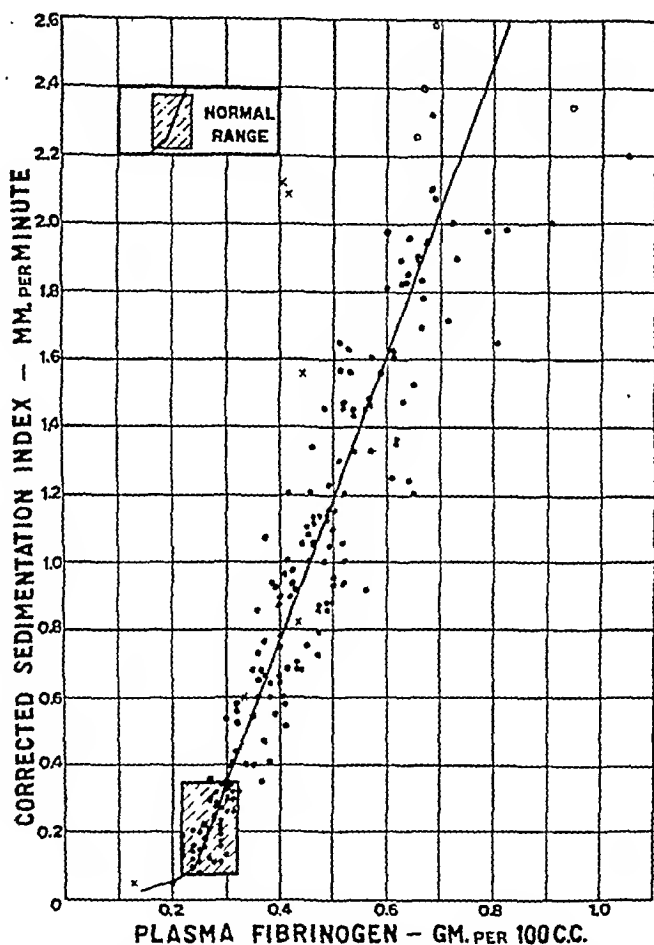


FIG. 1.—The relationship between the corrected sedimentation index and the fibrinogen content of the plasma in 190 instances, representing 39 different clinical diagnoses.

creases gradually during pregnancy and that there is a close relationship between the average fibrinogen values during the different months of pregnancy and the average sedimentation rates reported by Linzenmeier<sup>9</sup> for the same periods.

Because the plasma globulin content frequently is increased in the presence of infection,<sup>4,8</sup> several investigators have believed that increased sedimentation rates depend to a large extent on increased

concentration of plasma globulin. Plass and Matthew<sup>11</sup> observed, however, that the plasma globulin remains practically constant during pregnancy, and they believe that the increased fibrinogen content of the plasma plays the major rôle in the progressively increased sedimentation rate during the course of pregnancy. Furthermore, if blood from a patient with severe infection is defibrinated the rate of settling of the erythrocytes is almost negligible as compared to the rapid rate of settling of a non-defibrinated sample of the same blood.<sup>1,4</sup>

TABLE 1.—SUBJECTS STUDIED.

Diagnosis.	No. of tests.	Diagnosis.	No. of tests.
Normal . . . . .	40	Syringomyelia . . . . .	1
Lobar pneumonia . . . . .	10	Multiple sclerosis . . . . .	1
Bronchopneumonia . . . . .	4	Carcinoma at head of pancreas, jaundice . . . . .	1
Rheumatic fever, acute . . . . .	19	Abdominal carcinoma, site unde- termined, ascites . . . . .	1
Infection, acute respiratory . . . . .	4	Carcinoma of sigmoid . . . . .	4
Abscess of lung . . . . .	1	Osteosarcoma of ilium . . . . .	1
Injection abscess, syphilis . . . . .	1	Cholecystitis, chronic . . . . .	1
Pulmonary tuberculosis, active . . . . .	2	Ulcer of duodenum . . . . .	1
Fever (cause unknown) . . . . .	1	Rheumatic heart disease, compen- sated . . . . .	1
Multiple carbuncles . . . . .	1	Myxedema . . . . .	1
Empyema of pleura . . . . .	1	Exophthalmic goiter . . . . .	7
Influenza . . . . .	1	Osteogenesis imperfecta . . . . .	1
Arthritis, gonorrheal . . . . .	1	Herniorrhaphy . . . . .	27
Arthritis, infectious . . . . .	12	Common bile duct obstruction . . . . .	1
Hepatitis, acute . . . . .	6	Amputation . . . . .	3
Coronary thrombosis . . . . .	1	Appendectomy and removal of ovarian cyst . . . . .	1
Hodgkin's disease . . . . .	2	Ligation of Fallopian tubes . . . . .	1
Pansinusitis, acute . . . . .	1	Arspenamin dermatitis, syphilis . . . . .	1
Appendicitis, acute and appendec- tomy . . . . .	18		
Post-encephalitic paralysis agitans . . . . .	2		
Tumor of brain . . . . .	2		

The results obtained in 3 patients with acute hepatitis (Fig. 1) show essentially the same correlation between the plasma fibrinogen content and the corrected sedimentation index as was found for the other clinical conditions studied. In 1 of these patients the test was made shortly before death and showed both the plasma fibrinogen content and the corrected sedimentation index reduced below the normal limits (Fig. 1); in the other 2 patients the tests were made early in the illness. In 2 additional patients the tests were made after recovery from acute hepatitis and the corrected sedimentation index was observed to be increased disproportionately to the increase in the plasma fibrinogen (Fig. 1, indices 1.56, 2.08 and 2.12, indicated by crosses). The results in these 2 patients are in harmony with the findings of Bendien and Snapper<sup>1</sup> who reported increased sedimentation rates (Westergren's method<sup>15</sup>) in the presence of normal plasma fibrinogen values in certain cases of cirrhosis of the liver. These investigators found that the rate of settling of the erythrocytes of the defibrinated blood from these patients with cirrhosis of the liver was much more rapid than the rate of

settling of the erythrocytes of the defibrinated blood from patients with no liver involvement. The results of Bendien and Snapper and the observations above suggest, therefore, that the increase in the sedimentation rate found in these special cases\* is due in part to factors other than the fibrinogen content of the plasma.

That the plasma globulin and albumin content, the concentration of other colloids and crystalloids, and the plasma viscosity have some effect on the erythrocyte sedimentation rate is well recognized. The degree of correlation obtained between the fibrinogen content of the plasma and the corrected sedimentation index (Fig. 1) indicates, however, that the plasma fibrinogen content is the major factor which determines the corrected sedimentation index in the majority of cases. The explanation for this relationship must rest on the physicochemical properties of the plasma fibrinogen in respect to its effect on red cell aggregation;<sup>4</sup> the greater the plasma fibrinogen content, the greater the size of the settling red cell aggregates with a consequent greater speed of erythrocyte sedimentation.

**Summary.** 1. One hundred and ninety simultaneous measurements of the fibrinogen content of the plasma and the "corrected sedimentation index" were made in normal individuals and in patients with various kinds and degrees of pathologic conditions.

2. A close correlation was observed between the plasma fibrinogen content and the corrected sedimentation index.

3. In certain cases with liver damage the corrected sedimentation index is increased disproportionately to the increase in plasma fibrinogen content.

4. The results of the investigation indicate that, except in certain cases with liver damage, the plasma fibrinogen content plays the major rôle in controlling the corrected sedimentation index.

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## VITAMIN THERAPY IN PULMONARY TUBERCULOSIS.

## V. THE EFFECT OF VIOSTEROL ON THE DIFFUSIBLE AND NON-DIFFUSIBLE CALCIUM OF THE BLOOD AND SPINAL FLUID.

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It is the consensus of opinion that cerebrospinal fluid is that part of the blood which diffuses through the capillary walls and endothelial membranes of the choroid plexus. Thus it represents the diffusible fraction of calcium in the blood. Several investigators have used semipermeable membranes for testing the diffusibility of calcium *in vitro*. Their results have varied with the differences in the permeability of the respective membranes.

**Methods.** Serum and spinal fluid calcium was determined by the Clark and Collip<sup>1</sup> method, modification of Kramer and Tisdall.<sup>2</sup> Phosphorus determinations were made by the method of Benedict and Theis.<sup>3</sup> The serum and spinal fluid were obtained simultaneously at the same time of day. Determinations were performed immediately.

**Historical Data.** The results of numerous investigators (4 to 23) are compiled in Table 1.

In 20 normal cases we found the spinal fluid calcium to be 5.7 mg. per 100 cc., while in the same series the serum calcium averaged 11.1 mg. In 25 cases of pulmonary tuberculosis we found the spinal fluid calcium to be 6.2 mg. and the serum calcium to be 11.2 mg. In the same series of normal individuals, the serum phosphorus averaged 4.2 mg. and the spinal fluid phosphorus 1.9 mg. per 100 cc. The same values for phosphorus were found in the blood and spinal fluid in the 25 cases of pulmonary tuberculosis. In 41 normal individuals Cohen<sup>24</sup> found the phosphorus range in the spinal fluid to be 1.25 to 1.90 mg., with an average of 1.64 mg. per 100 cc.

**Diffusible Calcium.** Viosterol increases the absorption and retention of calcium.<sup>25</sup> Serum calcium is one of the indices of this physiological mechanism. The question arises as to whether viosterol increases the diffusible or the non-diffusible calcium. Agreeing with Cameron and Moorhouse,<sup>17</sup> we use the preceding terms rather than the terms "ionized" and "ionic" calcium as used by Vines.<sup>26</sup> According to them diffusible calcium is that fraction which includes calcium ions and unionized inorganic calcium compounds which can diffuse through a normally functioning animal membrane.

Rona and Takahashi<sup>27</sup> found that 65 to 75 per cent of the serum calcium of the horse, pig and cow is dialyzable with membranes;

TABLE 1.—COMPARISON OF SERUM CALCIUM WITH SPINAL FLUID CALCIUM IN NORMALS AND IN PATHOLOGIC CASES.

No. of cases.	Examiner.	Type of case.	Mg. per 100 cc.	
			Serum calcium.	Spinal fluid calcium.
20	Mestrezat	Normals	....	7.1
4	Kummer and Minkoff	Normals	....	5.0-5.2
12	Leieher	Normals	11.4	5.0
..	Depisch and Richter-Quittner	Normals	....	2.5
3	Pineus and Kramer	Normals	10.5	4.8
38	Critchley and O'Flynn	Normals	....	6.1
59	Neustaedter, <i>et al.</i>	Normals	....	5.8
68	Cantarow	Normals	9.2-11.0	4.5-5.5
20	Crimm and Strayer	Normals	11.1	5.7
	Normal average		10.8	5.2
2	Schmidt	Hydrocephalus (Adult)	....	15.3
		(Fetus)	....	7.0
1	Yvon	(Fetus)	....	8.0
1	Mestrezat	" (After death)	....	6.2
25	Halverson and Bergeim	Various diseases	....	5.1
1	Halverson and Bergeim	Paralytic dementia	....	6.0
12	Mann	Epileptics	....	8.0-9.0
6	Mann	Non-epileptics		
27	Weston Howard	Manic- Depr. Insanity		
		(Excited)	....	5.2
		(Depressed)	....	5.4
..	Leieher	Intracranial pressure (various)	....	4.7-5.7
..	Barrio	Cerebrosp. syph.	....	4.6-6.1
77	Critchley and O'Flynn	Pathologic	....	5.2-8.0
20	Cameron and Moorhouse	*Dogs. Normal	11.1	5.8
17	Nourse, Smith and Hartman	Spasmophilia (following cure)	9.9	4.8
17	Hamilton	Epilepsy	9.6-12.8	4.4-6.6
9	Merritt and Bauer	Pul. tuberc.	9.0	4.6
22	Cooper	Pul. tuberc.	10.4	4.8
18	Booth and Broga	Pul. tuberc.	9.4-16.3	5.2-7.6
25	Crimm and Strayer	Pul. tuberc.	11.2	6.2
	Pathologic average		10.7	6.4

\* Not included in average

von Meysenbug, Pappenheimer, Zucker and Murray<sup>28</sup> obtained 60 to 70 per cent for normal men and dogs; Cruikshank,<sup>29</sup> 55 to 70 per cent in dogs. Loeb<sup>30</sup> found 55 to 75 per cent calcium diffusible against distilled water, and a pH of 7.4; Tischimber,<sup>31</sup> 50 to 60 per cent; Cushny,<sup>32</sup> by ultrafiltration obtained 62 to 70 per cent. Moritz<sup>33</sup> found the diffusible fraction of serum calcium in rabbits to average 56 per cent although Updegraff, Greenberg and Clark<sup>34</sup> cor-

rected his data to average 68 per cent. Lui<sup>35</sup> obtained values ranging from 42.5 to 48 per cent of the total serum calcium. Neuhausen and Pincus<sup>36</sup> found that 50 to 75 per cent of pig serum calcium is diffusible.

Vines<sup>26</sup> concluded that diffusible calcium is about 63 per cent of the plasma calcium. Cameron and Moorhouse<sup>17</sup> stated that the average true diffusible calcium of blood plasma in normal dogs was 53 per cent of the serum calcium value. Cantarow<sup>23</sup> found the diffused calcium to be about 45 to 55 per cent of the total calcium.

In a series of 20 normal individuals we found that the diffusible calcium represented 51 per cent of the total serum calcium. In 25 cases of pulmonary tuberculosis, the majority being of an exudative type, the diffusible calcium averaged 55 per cent of the serum calcium. Booth and Broga<sup>22</sup> and Cantarow<sup>23</sup> found an increased diffusibility ratio in this type of pulmonary tuberculosis, that is, ratio of diffusible to non-diffusible calcium.

**The Diffusibility Ratio.** Table 2 presents an analysis of 10 cases of pulmonary tuberculosis. Specimens for the determinations were taken at the same time of the day. The average serum calcium was 11.1 mg., while the spinal fluid calcium was 6.1 mg. per 100 cc. Phosphorus in the serum was 4.6 mg., while the phosphorus in the spinal fluid was 2.1 mg. per 100 cc. The diffusibility ratio for the 10 cases averaged 127 per cent. Five of the cases which had a serum calcium value of 11.7, 10.8, 12.1, 12.4 and 11.8 mg. per 100 cc. respectively, were chronically ill. The other 5 cases were acutely ill. None of the cases presented symptoms of intestinal tuberculosis. The 5 subjects who were chronically ill had an average diffusibility ratio of 90 per cent, while the 5 acutely ill averaged 165 per cent.

TABLE 2.—THE BLOOD SERUM AND SPINAL FLUID CALCIUM OF TEN CASES OF PULMONARY TUBERCULOSIS.

Case No.	Blood serum.				Spinal fluid.				D/ND ratio.†	
	Before viosterol.		After viosterol.		Before viosterol.		After viosterol.		Before viosterol.	After viosterol.
	Ca.*	P.*	Ca.*	P.*	Ca.*	P.*	Ca.*	P.*		
1156	10.9	4.9	13.3	4.6	7.6	2.0	7.1	2.9	230	114
1146	10.6	5.5	16.3	6.6	6.2	2.9	6.8	2.8	140	71
1140	9.4	4.4	15.4	5.6	6.0	2.3	6.6	2.3	176	75
1134	11.7	4.8	15.5	5.0	5.5	2.4	6.4	2.6	88	70
1130	10.8	4.4	16.6	5.6	5.2	1.8	7.2	2.0	93	76
1115	12.6	4.4	15.0	4.3	6.5	2.0	6.6	2.3	106	78
1012	12.1	4.7	17.1	5.2	5.3	1.9	7.3	1.7	78	74
1109	12.4	5.3	15.4	5.6	5.9	1.9	8.4	2.0	90	120
614	10.9	4.5	13.3	4.3	6.9	2.3	8.4	2.6	172	171
966	11.8	3.4	14.0	4.2	5.9	1.8	7.6	2.5	100	118
Average	11.1	4.6	15.1	5.2	6.1	2.1	7.2	2.4	127	96

\* Values expressed as milligrams per 100 cc. of serum or fluid.

† Ratio of diffusible to non-diffusible calcium expressed as percentage.

In the series of 25 cases of pulmonary tuberculosis, the diffusibility ratio averaged 139 per cent with a range of 82 to 315 per cent. In the 20 normal individuals previously mentioned the diffusibility ratio averaged 104 per cent with a range of 82 to 160 per cent.

In 63 cases of pulmonary tuberculosis, Cantarow<sup>23</sup> found the diffusibility ratio to range from 56.7 to 152 per cent. Cooper<sup>21</sup> in 10 cases of pulmonary tuberculosis, exudative type, reported a diffusibility ratio of 88 per cent and in 12 cases of the productive type a diffusibility ratio of 87 per cent. Booth and Broga<sup>22</sup> determined in 18 cases of pulmonary tuberculosis a diffusibility ratio of 50 to 158 per cent. In the 11 cases of pulmonary tuberculosis, proliferative type, studied by Cantarow,<sup>23</sup> the diffusibility ratio was below 100 per cent in 9 of the cases; the decrease in the diffusibility ratio was attributed to a primary increase in non-diffusible calcium.

**The Effect of Viosterol on the Diffusible and the Non-diffusible Calcium.** In our series of 25 cases, 1, fibroid type, had a diffusibility ratio of 315 per cent. This was due to a decrease in non-diffusible calcium, the serum calcium being 8.3 mg. and the spinal fluid calcium 6.3 mg. per 100 cc. This patient received viosterol 250 D,\* 1.5 cc. (60 gtts.) q. d. for 4 weeks. At the end of this viosterol period the diffusibility ratio had decreased from 315 to 102 per cent, due to an adequate absorption of calcium.

Another case, fibroid type with chronic bronchitis, had a diffusibility ratio of 236 per cent, due to a high diffusible calcium content, the serum calcium being 11.1 mg. and the spinal fluid being 7.8 mg. per 100 cc. For a period of 3 weeks, viosterol 10,000 X †, 0.5 cc. (20 gtts.) q. d., reduced the diffusibility ratio from 236 to 93 per cent. After viosterol was discontinued an increase in the non-diffusible calcium was accompanied by a decrease in the diffusible calcium. It is advisable to use 250 D to accomplish this result. Most cases do not tolerate 10,000 X for a longer period than 8 days.

In 10 cases of pulmonary tuberculosis (Table 2), the normal calcium averaged 11.1 mg. and the phosphorus 4.6 mg. per 100 cc. Following the administration of viosterol 10,000 X the average serum calcium rose to 15.1 mg. and the phosphorus to 5.2 mg. per 100 cc. The spinal fluid calcium was determined at the same time and the diffusible calcium for this series averaged 6.1 mg. and the phosphorus 2.1 mg. per 100 cc. After the administration of viosterol 10,000 X, the calcium rose to 7.2 mg. and the phosphorus to 2.4 mg. per 100 cc. Diffusible calcium represented 55 per cent of the total calcium before the administration of viosterol. The spinal fluid or diffusible calcium represented 47 per cent of the total serum calcium after the administration of viosterol. The average diffusibility ratio prior to the administration of viosterol equaled

\* 10,000 International Units per gram.

† 10,000 times average cod-liver oil, 1,000,000 International Units per gram; kindly supplied by Mead Johnson & Co.

127 per cent. After viosterol, 10,000 X, 0.5 cc. (20 gtt.) q. d., over a period from 8 to 15 days, the diffusibility ratio dropped to 96 per cent.

**Comment.**—It is obvious that viosterol increases most markedly the non-diffusible calcium and to a lesser extent the diffusible calcium. This is confirmed by a decrease in the diffusibility ratio which accompanies the administration of viosterol in cases of pulmonary tuberculosis.

It is evident that the untreated patient acutely ill with pulmonary tuberculosis has an increased diffusibility ratio, providing his intake and absorption of calcium and phosphorus is adequate. Likewise the patient, whose tuberculosis presents considerable healing and fibrosis, has a tendency toward a lower diffusibility ratio. Cantarow<sup>23</sup> states that the diffusibility ratio associated with a fibrotic lesion of low-grade activity is a subnormal one. We are inclined to assume that it is not subnormal, but rather one which approaches the diffusibility ratio of an individual with a normal calcium metabolism.

In previous work,<sup>37</sup> we observed that a more rapid clearing and fibrosis was evident in some cases of pulmonary tuberculosis after viosterol had been administered. An increase in non-diffusible calcium is present in patients with fibrotic lesions. Therefore these observations lead us to conclude that an increase in non-diffusible calcium favors the healing of pulmonary tuberculosis.

**Summary.** 1. Viosterol increases the calcium in the blood and spinal fluid of patients with pulmonary tuberculosis.

2. Viosterol increases both the diffusible and non-diffusible fractions of calcium. The non-diffusible fraction is the more affected.

3. In patients with pulmonary tuberculosis, viosterol reduces the diffusibility ratio by increasing the non-diffusible calcium.

Grateful acknowledgement and thanks are due Miss Grace Heimann of Boehne Hospital Laboratory for her valuable assistance.

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## REVIEWS.

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APPENDICITIS. ITS ÆTIOLOGY AND PATHOLOGY. By LUDWIG ASCHOFF, Freiburg i. Br. With a Short Contribution on the Lymphatic System of the Human Appendix by DR. H. SENG. Translated by G. C. PETHER, M.D., M.R.C.P. Pp. 153; 36 illustrations. London: Constable & Co., Ltd., 1932. Price, 16/-.

THIS develops the view that appendicitis starts from an epithelial lesion, the inflammation spreading both as a phlegmon on the mucosa and as a wedge toward the serosa, with rapid longitudinal spread in the muscularis and serosa. It opposes Ricker's theory (1924), that the trouble is due to a reflex irritation of the nerves of the appendiceal vessels. Special attention is given in Dr. Seng's section to the peculiar lymphatic arrangement as supporting the above theory. The evidence for a special bacterial flora (non-hemolytic streptococci and pneumococci) in the distal portion as chief exciting causes is given in detail. While of great interest and strongly suggestive, it hardly warrants the deduction that the group of the intestinal streptococcus "may be regarded as *the* cause of appendicitis." As the same organisms are found in normal appendices, a hypothetical increase in virulence is invoked, favored by a stagnation of the secretion of the distal portion. In view of recent increases in appendiceal morbidity and mortality, this thorough presentation, well translated, merits careful study by practitioners even more than by pathologists.

E. K.

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THE BRAIN AND ITS MECHANISM. By SIR CHARLES SHERRINGTON, O.M., G.B.E., F.R.S., Waynflete Professor of Physiology in the University of Oxford. The Rede Lecture delivered before the University of Cambridge, December 5, 1933. Pp. 35. New York: The Macmillan Company, 1933. Price, 50 cents.

THIS Rede Lecture at the University of Cambridge develops the picture of the brain as a wide nerve net made up of nerve threads with two kinds of action at the nodal points, one which fires the action of the thread (motor impulse), the other which impedes the firing. The travelling signal (excitant here indistinguishable from inhibitant) has been shown by Adrian to be "a brief local depolarization of the electrically polarized surface layer of the nerve thread." Yet the author does not presume to explain the manifold activities of the mind and affirms that the problem will long offer the clinically somewhat cold comfort that to journey is better than to arrive.

E. K.

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THOMAS YOUNG, F.R.S., PHILOSOPHER AND PHYSICIAN. By FRANK OLDHAM, M.A., B.Sc., A. Inst. P., formerly Scholar of St. John's College, Cambridge. Pp. 159; illustrated. New York: Longmans, Green & Co., 1933. Price, \$2.40.

TO the reader who has known in a vague way that Sir Thomas Young was one of the greatest scientists of 150 years ago this concise but detailed account of his career and achievements will be a welcome acquisition.

Born of Quaker parents in the West Country, he could read at the age of 2, and knew "The Deserted Village" by heart at 6. An accomplished classicist and linguist, he has mastered Linnæus, Newton and Lavoisier as well as his Corneille and Racine at 17. Before his death from arteriosclerosis at 56, he had elucidated the mechanism of accommodation, discovered astigmatism, established his Modulus (numerical ratio of stress to strain in a stretched material), advanced the wave theories of light and sound by his study of interference phenomena, discovered the eriometer principle of optically measuring the size of small particles, through his study of capillarity and cohesion made the first estimate of the size of atoms, and anticipated Champollion in most of the interpretation of the famous Rosetta stone. Truly an intellectual giant who fully deserves the words on his tablet in Westminster Abbey: "A man alike eminent in almost every branch of human learning."

E. K.

NATURE AND NURTURE. By LANCELOT HOGGEN, M.A., D.Sc., Professor of Social Biology, University of London. Pp. 143. New York: W. W. Norton & Co., Inc., 1933. Price, \$2.75.

METHODS are presented for studying human genetics and evaluating the relative influences of heredity and environment. Emphasis is placed on genetics as a branch of medicine; therefore, the behavior of the genes which determine mental defects and susceptibility to diseases are known. Incurable so far is stressed. Already more than 30 such diseases are known. The scope of the book is indicated by the chapter headings. Chapter I treats of the medical applications of genetical principles; those which follow with the solutions of the problems involved. Thus Chapter II deals with the "application and limitations of the theory of random mating," Chapter III with "consanguineous parentage and the theory of inbreeding," Chapter IV with "the genetic analysis of familial diseases," and Chapter V with "the interdependence of nature and nurture." An analysis of human linkage data is given in one of the appendices.

Statistical methods are given for analyzing data from slow breeding organisms with few offspring where the matings are not controlled by the investigator. The methods are applied with a clear recognition of the fact that the accuracy of the conclusions drawn cannot exceed that of the assumption and hypotheses on which they are based. Thus the author points out that the assumption of random mating is not valid in certain cases, since gentlemen are reputed to prefer blondes. Or again, "A young woman with a strong belief in the sprinkling of babies may be inclined to reject the advances of a young man with an equally strong conviction in favor of immersion of the presence of obvious physical defects form evident exceptions. Nevertheless, the assumption of random selection appears to be applicable generally in regard to characteristics which are not readily recognizable such as taste-blindness or isoagglutinins in the blood. The author states: "First it is necessary to establish the principle of random mating. Then we shall examine when it can be used successfully. Finally we must examine when it breaks down. A scientific law is only correctly stated when it contains within itself a recognition of its own limitations. The treatment of the evidence derived from a study of identical twins is the least satisfactory part of the book and needs to be buttressed by a study of the results obtained in this country by Newman and his coworkers. This book presents a well-considered approach to the subject and is worthy of the attention of physicians, medical students and students of human heredity."

E. C.

THE ROSE RESEARCH ON LYMPHADENOMA. First Volume. By SIR THOMAS HORDER and others. Pp. 136; 98 illustrations, many in color. Baltimore: William Wood & Company, 1933. Price, \$7.25.

THE riddle of the etiology of Hodgkin's disease, called lymphadenoma in England, has remained unsolved since Thomas Hodgkin first described it in 1832. This volume records the results of work carried on between 1920 and 1930 at St. Bartholomew's Hospital, under the Rose Foundation, and since then under the Medical Research Council. The text opens with a brief but lucid description of Hodgkin's disease in its typical and atypical forms. H. M. Gordon's section on etiology describes the negative studies on spirochetes, fungi and tubercle bacilli.

In marked contrast to these negative studies was the search for a virus. Sterile broth suspensions of glands removed at biopsy were made; subcutaneous injection into rabbits yielded only inflammatory nodules. But when a 1 to 10 suspension, which had been macerated in the icebox for some days, was injected intracerebrally into rabbits, a striking syndrome of ataxia and spastic paralysis of the hind legs appeared in 2 to 6 days followed by wasting of these limbs and, in some cases, death of the animal. As controls, glands from cases of sarcoma, carcinoma, lymphatic leukemia, adenitis and hyperplasia were subjected to the Gordon test. None of these produced the encephalitis-like syndrome in rabbits.

The pathogenic agent appeared to be a virus of the same class as that of vaccinia. Tests on its filterability have been so far inconclusive.

By special mordants and stains, small granules similar to the Paschen bodies, which many believe to be the case of vaccinia, were found; this is suggestive but not conclusive. The agent withstands heat, phenolation and desiccation very well. It will not transmit in series. It appears to be limited to glands from cases of Hodgkin's disease, and its presence, as revealed by rabbit test, will be useful for purposes of diagnosis, especially in obscure cases where the histologic picture is inconclusive.

The description of the lesions produced in the brain of rabbits injected with this organism is not very extensive. The lesions that are produced consist of a round-cell infiltration into the meninges and, around some of the bloodvessels in the cortex, a perivascular exudate of lymphocytes.

The third section of the book concerns the division of yeasts by complement-fixation methods into a limited number of serologic types. They appear to have nothing to do with lymphadenoma.

In the next section—blood studies of experimental animals—the evidence indicates that nothing of value can be learned from the hemoglobin and red blood corpuscles, but that the behavior of the leukocytes may prove to be useful.

The last section of the book, by B. D. Pullinger, describes the histology and histiogenesis of the disease in which the author supports the theory that the reticulum is the responsible tissue element in the construction of Hodgkin's disease and that endothelial cells are of no consequence. He adduces some evidence that the term reticuloendothelium is incorrect and inappropriate.

This is a handsome volume, well printed and finely illustrated. It is not a book for the general practitioner but is indispensable to one who desires to know thoroughly the recent work on Hodgkin's disease or who contemplates making use of the Gordon test as a diagnostic measure. It is to be regretted that some of the writers have not employed the elegant and attractive English that makes writings from their country so welcome and that develops scientific literature that reads like fiction. It may well be that the highly technical character of this discussion makes it difficult to use choice language, but a dry subject is often made easy of reading and understanding by elegant style.

H. F.

**BENIGN TUMORS IN THE THIRD VENTRICLE OF THE BRAIN: DIAGNOSIS AND TREATMENT.** By WALTER E. DANDY, M.D., Adjunct Professor of Surgery, The Johns Hopkins University. Pp. 171; 120 illustrations. Springfield, Ill.: Charles C Thomas, 1933. Price, \$5.00.

THIS monograph consists of 21 case reports from the author's surgical records of benign tumors in the third ventricle, including colloid cysts. Each case is excellently illustrated with photographs, ventriculograms and diagrams, by means of which the reader accompanies the author step by step through diagnosis and operative procedure. The importance of the ventriculogram in diagnosis is stressed. The book concludes with a chapter on analysis of signs and symptoms produced by these tumors.

M. McC.

**THE CANCER PROBLEM AND ITS SOLUTION.** By HASTINGS GILFORD, F.R.C.S. Pp. 59. London: H. K. Lewis & Co., Ltd., 1934. Price, Cloth, 2s 6d; Paper, 1s 6d.

PROCEEDING from the axiom that the cancer cell is a dedifferentiated cell, the result of premature degeneration of animal (human) tissue, the author urges that the fight against cancer be concentrated on the "degenerating circumstances which anticipate or prolong the course of degeneration and favor the occurrence of precancers." Specifically he considers an easy but not sternly practical philanthropy and an efficient sanitation (which increase the survival and reproduction of the unfit) and a disregard of Darwin's evolutionary principles, especially of the need for use as a requisite of development, as the chief contributory errors. The logical sequence of wider application of the tenets of eugenics or wholesale sterilization of the supposedly unfit are not mentioned. Considered strictly from the above point of view the book is stimulating. To the reader, especially the cancer student, it is not recommended that the assemblage of facts or the deductions therefrom be too closely analyzed.

E. K.

**WILHELM CONRAD RÖNTGEN AND THE EARLY HISTORY OF THE ROENTGEN RAYS.** By OTTO GLASSER, Cleveland Clinic Foundation. With a Chapter "Personal Reminiscences of W. C. Röntgen" by MARGRET BOVERI, Berlin. Pp. 494; 96 illustrations. Springfield, Ill.: Charles C Thomas, 1934. Price, \$6.00.

IN 1931, the author brought out through Springer the German edition of the work which he has now translated, revised and enlarged in response to numerous requests. With material collected principally from the literature of 1896, the author plunges *in medias res* with an account of the great discovery. Unlike many that have had to wait years for recognition, it was heralded and confirmed throughout the civilized world even before its discoverer had spoken publicly about it (January 23, 1896, to the Physical Medical Society of the University of Würzburg). It is only in the 5th chapter that we come to the scientist and the man, to be followed by an especially sympathetic chapter of personal reminiscences by Margret Boveri. His modesty and reticence (he gave no lecture on receiving the first Nobel physics prize) are apparent throughout and the war gloom, with his death in 1923 during the inflation, carries its lesson. Chapters on the Roentgen rays in physics, in warfare, medical diagnosis and therapy and in non-medical directions add to the reader's interest in this extremely valuable record. In Chapter 23, the bibliography gives the astonishing number of 1044 books and pamphlets published on the subject in 1896 alone.

E. K.

THE THERAPEUTIC AGENTS OF THE QUINOLINE GROUP. By W. F. VON OETTINGEN, M.D., Ph.D. Assistant Professor of Pharmacology, School of Medicine, Western Reserve University. Pp. 301. New York: The Chemical Catalog Co., Inc., 1933. Price, \$6.00.

IN this American Chemical Society Monograph, the material is intended primarily for chemists and pharmacologists, but the presentation, involving structural formulæ and common as well as technical names, is such that the average physician will have no difficulty in following it. Emphasis is placed upon pharmacological actions and chemical details are omitted. Since some of these drugs are in everyday use (notably quinin, quinidin, and cinchophen), others represent high hopes that were not substantiated by wider experience (such as plasmochin and yatren), and others may be a starting point for new groups of local anesthetics (as nupercain), and anti-septics (the acridin dyes), physicians and surgeons will find much to interest them in this admirable monograph. C. S.

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BIRTH CONTROL IN PRACTICE. Prepared Under the Supervision of a Scientific Advisory Committee. Text and Tables by MARIE E. KOPP, Ph.D. With a Foreword by ADOLF MEYER, M.D. Pp. 290; 50 tables. New York: Robert M. McBride & Co., 1934. Price, \$3.75.

THIS book, although obviously written for propaganda purposes, has the merit of confining itself strictly to the facts it presents. The text is rigidly factual, no opinions are expressed by the author, and it is a most accurate statistical report based on 10,000 cases of various aspects of the work in a large birth control clinic. Of special interest to those concerned in the Birth Control movement, it gives a precise account as to just what can and cannot be accomplished with modern contraceptive methods in a "Maternal Health Center."

The text is divided into six parts. The first is historical and descriptive. The second section deals with the pertinent aspects of the patient's social and economic history. Part three concerns itself with an analysis of the patient's various physical factors such as sex history, obstetric history, studied by the statistical method, much of which in my opinion might well be omitted. The frequency of abortions (69% induced) is evidenced by the statement that "more than 1 in 4 pregnancies was terminated spontaneously or was intentionally interrupted." In part four, the one weak feature is an unconvincing summary of the medical indications for prescribing contraceptives. The technique of the various contraceptive methods prescribed at the clinic is well given together with an illuminating compilation of the results that have been secured. Here lies the real justification for the book, as it sticks rigidly to facts, and such questions as how often will the ignorant and illiterate use contraceptive methods, how effective is one method compared to another, etc., can be answered with accuracy from a series of cases large enough to eliminate the personal equation.

The book closes with a good summary and a series of statistical tables.

O. T.

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LIFE OF CHRISTIAN SAMUEL HAHNEMANN. Founder of Homœopathy. By ROSA WAUGH HOBHOUSE, with a Preface by SIR JOHN WEIR, K.C.V.O., M.B. Pp. 288; illustrated. London: The C. W. Daniel Company, 1933. Price, 7/6.

HAHNEMANN was undoubtedly sincere in his effort to learn "if God had not indeed given some certain law by which the diseases of mankind could be cured." Undoubtedly, also, the harmless methods of treatment

that he advocated were of great importance in combating the harmful polypharmacy that had so long existed. Thus his name will live in medicine's story, and whether or not the reader agrees with the principles of homeopathy, he will surely be interested in this clear portrayal of a consecrated life. Many too will doubtless be surprised to read that Hahnemann regarded removal or destruction of the fundamental cause of the disease "as the most elevated way that practical medicine could follow if it had sufficient knowledge." ("Curative Power of Drugs.") Also he recognizes that if fundamental knowledge of the cause of an acute disease and how to remove it be lacking, the symptoms may properly be combated by "temporary remedies . . . which produced an opposite condition." ("Organon.") The arguments for *similia similibus* and the increasing potency of increasing dilutions ("potentisation"), it must be confessed, seem painfully weak; neither does the attempt to use the Arndt-Schulz law as a support seem justified. As a demonstration of the truth of homeopathic philosophy, this book does not carry conviction; as a portrayal of an extraordinary personality and an important development in 19th century medicine, it is well worth while.

E. K.

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RECENT ADVANCES IN ENDOCRINOLOGY. By A. T. CAMERON, M.A., D.Sc. (Edin.), F.I.C., F.R.S.C., Professor of Biochemistry, Faculty of Medicine, University of Manitoba; Biochemist, Winnipeg General Hospital. Pp. 365; 54 illustrations, including 2 plates. Philadelphia: P. Blakiston's Son & Co., 1934. Price, \$3.50.

THE rapid changes and advances in this complex subject make a "Recent Advance" volume particularly useful, especially as endocrinology is a topic which seems to lend itself easily to romance. The author has achieved his difficult task well. Anatomy, physiology, pathology, medicine and surgery have all contributed their quota to knowledge here detailed of the various endocrine organs in health and disease. To this the 801 references testify—a good half of these apparently being from the present decade. The final chapter on Interrelations is especially to be commended for its sanity and conservatism.

E. K.

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AMERICAN UNIVERSITIES AND COLLEGES. Edited by JOHN HENRY MACCRACKEN, for the American Council on Education, Washington, D. C. Pp. 1066. Second edition, revised and enlarged. Baltimore: The Williams & Wilkins Company, 1932. Price, \$4.00.

THIS *multum in parvo* presents not only a general exposition of American higher education (284 pages) but also details of organization, requirements, resources, size of faculties, attendance, degrees conferred, etc., of the 521 accredited institutions (690 pages). The 17 appendices are concerned with the American Council on Education (by whom the book was prepared), 9 other educational associations, and, last but not least, more than 2 pages of the various university degrees mentioned in the volume. Since the 1st edition (1928), 126 institutions have been added and the data of the rest submitted to their own officials for correction. Nevertheless, or perhaps on this account, there is a distinct lack of uniformity in presenting the pictures, especially of the larger institutions, tending to difficulties of comparison at least for the casual reader. One can safely say, however, that the book accomplishes its purpose of supplying an accurate and comprehensive picture of American higher education.

E. K.

## BOOKS RECEIVED.

## NEW BOOKS.

*Appendicitis. Its Aetiology and Pathology.* By LUDWIG ASCHOFF, Freiburg i. Br. With a Short Contribution on the Lymphatic System of the Human Appendix by DR. H. SENG. Translated by G. C. PETHER, M.D., M.R.C.P. Pp. 153; 36 illustrations. London: Constable & Co., Ltd., 1932. Price, 16/- (Review, p. 563.)

*The Renaissance of Medicine in Italy.* By ARTURO CASTIGLIONI, M.D., Professor of the History of Medicine at the University of Padua. The Hideyo Noguchi Lectures. Publications of the Institute of the History of Medicine, The Johns Hopkins University, Third Series, Volume 1. Pp. 91; 1 illustration. Baltimore: The Johns Hopkins Press, 1934. Price, \$1.50.

*Alcohol. Its Effect on Man.* By HAVEN EMERSON, M.D., Professor of Public Health Practice, Columbia University. Pp. 114. New York: D. Appleton-Century Company, 1934. Price, \$1.00.

*The Cancer Problem and Its Solution.* By HASTINGS GILFORD, F.R.C.S. Pp. 59. London: H. K. Lewis & Co., Ltd., 1934. Price, cloth, 2s 6d; paper, 1s 6d. (Review, p. 566.)

*Mystery Magic and Medicine.* By HOWARD W. HAGGARD, M.D., Associate Professor of Applied Physiology, Yale University. Pp. 192; illustrated. Garden City, N. Y.: Doubleday, Doran & Co., 1933. Price, \$1.00.

*Jubilee Edition, Deutsche medizinische Wochenschrift, January 5, 1934.* Pp. 88; illustrated, some colored. Leipzig: Georg Thieme, 1934.

Articles by v. Krehl, Kolle, Aschoff, Umber, Heine, Morawitz and others only less well known make this, indeed, a noteworthy jubilee number. A beautiful colored plate of inflammations of the iris demands attention even under the concealing title of *Regenbogenhaut*.

*The Anatomy of the Rhesus Monkey (Macaca mulatta).* By various contributors. Illustrated by BENJAMIN KOPEL. Edited by CARL G. HARTMAN, Department of Embryology, Carnegie Institution of Washington, and WILLIAM L. STRAUS, JR., Department of Anatomy, The Johns Hopkins University, Baltimore. Pp. 383; 125 illustrations. Baltimore: The Williams & Wilkins Company, 1933. Price, \$6.00.

*Human Sex Anatomy.* By ROBERT LATOU DICKINSON, M.D., F.A.C.S. Pp. 145; more than 1000 illustrations. Baltimore: The Williams & Wilkins Company, 1933. Price, \$10.00.

*The Medical Clinics of North America, Volume 17, No. 1 (Cleveland Clinic Number—January, 1934).* Pp. 253; 53 illustrations. Philadelphia: W. B. Saunders Company, 1934. Price, Clinic Year: paper, \$12; cloth, \$16.

*The Brain and Its Mechanism.* By SIR CHARLES SHERRINGTON, O.M., G.B.E., F.R.S., Waynflete Professor of Physiology in the University of Oxford. The Rede Lecture delivered before the University of Cambridge, December 5, 1933. Pp. 35. New York: The Macmillan Company, 1933. Price, 50 cents. (Review, p. 563.)

*Thomas Young, F.R.S., Philosopher and Physician.* By FRANK OLDHAM, M.A., B.Sc., A. Inst. P., formerly Scholar of St. John's College, Cambridge. Pp. 159; illustrated. New York: Longmans, Green & Co., 1933. Price, \$2.40. (Review, p. 563.)



*Annals of the Pickett-Thomson Research Laboratory, Vol. 9, Monograph XVI, Part I. Influenza.* By DAVID THOMSON, O.B.E., M.B., CH.B. (EDIN.), D.P.H. (CAMB.), Honorary Director, Pickett-Thomson Research Laboratory, St. Paul's Hospital, London, and ROBERT THOMSON, M.B., CH.B. (EDIN.), Pathologist to the Pickett-Thomson Research Laboratory. Pp. 640; 28 plates of illustrations, various charts and tables. Baltimore: The Williams & Wilkins Company, 1933. Price, \$12.50.

*Krebs im Lichte biologischer und vergleichend-anatomischer Forschung. 1. Band. Ektodermkrebs.* Pp. 192; 43 illustrations. Leipzig: Franz Deuticke, 1934. Price, M. 10.

### NEW EDITIONS.

*A Diabetic Manual.* By ELLIOTT P. JOSLIN, M.D., Clinical Professor of Medicine, Harvard Medical School; Medical Director, George F. Baker Clinic for Chronic Disease at the New England Deaconess Hospital, etc. Pp. 224; 49 illustrations. Fifth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1934. Price, \$2.00.

This very practical and entertainingly written book is invaluable to the diabetic patient in explaining to him clearly and scientifically the nature of his disease and the way in which his intelligent coöperation is vital in his treatment. Illustrations make vivid the explanations. This manual is of great value to the physician as well, in directing him in the ways of instructing his patients.

*Human Embryology and Morphology.* By SIR ARTHUR KEITH, M.D., F.R.S., LL.D., D.Sc., F.R.C.S. (ENG.), Master of the Buckston Brown Research Farm, etc. Pp. 558; 535 illustrations. Fifth edition. Baltimore: William Wood & Company, 1933. Price, \$10.00.

Recent advances, particularly in the interpretations put on the significance of observed facts, have required a thorough revision since the appearance of the last edition in 1923. A new chapter has been added on Spemann's localized embryonic areas known as "Organizers" and the chemical substances by which they exercise their influence. The relatively small print and concise style together with the eminence of the author combine to make this book a splendid source of reference.

*Fundamentals of Biochemistry.* By T. R. PARSONS, B.Sc. (LOND.), M.A. (CANTAB.), Sidney Sussex College, Cambridge. Pp. 435; 26 illustrations. Fourth edition. Baltimore: William Wood & Company, 1933. Price, \$3.00.

The fact that a fourth edition has appeared within a little over a decade speaks for the continued popularity of Parsons' work. This very useful little book is warmly to be recommended to those who would like a brief and modern account of the principles of biochemistry.

*Neuroanatomy.* By J. H. GLOBUS, B.S., M.D., Associate Professor of Neuropathology and Neuroanatomy, New York University and Bellevue Hospital Medical School, etc. Pp. 229; 37 text illustrations and 53 plates. Sixth edition, revised and enlarged. Baltimore: William Wood & Company, 1934. Price, \$3.50.

The author in the preface to the first edition makes this statement: "The structure of the central nervous system is considered by many a student and teacher as the most intricate and difficult branch of human anatomy. This unjustified belief is very likely the result of the old methods of approaching the subject of neuroanatomy." The appearance of a sixth edition of Globus' book indicates that he has succeeded in providing a guide which many have found useful.

*American Universities and Colleges.* Edited by JOHN HENRY MACCRACKEN, for the American Council on Education, Washington, D. C. Pp. 1066. Second edition, revised and enlarged. Baltimore: The Williams & Wilkins Company, 1932. Price, \$4.00. (Review, p. 568.)

*Laboratory Medicine.* By DANIEL NICHOLSON, M.D., Member of the Royal College of Physicians, London; Assistant Professor of Pathology, University of Manitoba, etc. Pp. 566; 124 illustrations. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1934. Price, \$6.50.

*Hypertension and Nephritis.* By ARTHUR M. FISHBERG, Associate Professor to Beth Israel Hospital; Associate in Medicine, Mount Sinai Hospital, New York City. Pp. 668; 39 illustrations and 1 colored plate. Third edition, thoroughly revised. Philadelphia: Lea & Febiger, 1934. Price, \$6.50.

*Traitement des Maladies Rhumatismales par la Sanocrysine.* By KNUD SECHER, Médecin-Chef à l'Hôpital de Bispebjerg, Copenhagen. Pp. 84; 25 illustrations. Second edition. Copenhagen: Levin & Munksgaard, 1933. (Price not given.)

*A System of Clinical Medicine.* By THOMAS DIXON SAVILL, M.D., London. Edited by AGNES SAVILL, M.D., assisted by E. C. WARNER, M.D. Pp. 1063; 162 illustrations. Ninth edition. Baltimore: William Wood & Company, 1933. Price, \$9.00.

*Pfitzner's Leitfaden für Situsübungen an der Leiche.* By DR. MED. K. O. HENCKEL, Professor an der Universität Concepción (Chile). Pp. 36. Eighth edition. Leipzig: Franz Deuticke, 1934. Price, M. 1.20.

A compendium of the anatomy of the chest and abdomen; not suitable for use in this country.

# PROGRESS OF MEDICAL SCIENCE

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## GYNECOLOGY AND OBSTETRICS

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UNDER THE CHARGE OF  
CHARLES C. NORRIS, M.D.,  
PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE,  
UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.,

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FRANK B. BLOCK, M.D.,  
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### TREATMENT OF CANCER OF THE CERVIX.

BY FRANK B. BLOCK.

IN this brief review of the extensive recent literature on uterine cancer it is obvious that of contemporaneous opinion only a general summary may be presented; but an effort will be made to show the possibilities of treatment, supplemented when desirable by statistical confirmation. The importance of this subject appears in HIRST's (*J. Am. Med. Assn.*, 1933, 101, 897) address, in which he points out that 1 of every 8 women who reach the age of 35 will have a cancer and that the disease ranks second among the causes of death in America. The mortality is increasing, rising from 63 to 96 per 100,000 in 7 years (more than 50%). Of cancers in women, over 25% are in the genital organs, 80% of which are in the cervix uteri. Furthermore, of 4 women who come to a physician with cancer of the cervix, 1 may survive. Class I of the League of Nations classification of cancers of the cervix in which the disease is confined to that locality has a 50 to 80% 5-year recovery rate; Class IV, in which vagina, bladder and bowel are also involved, a rate of 2% or less. The whole problem of securing better results resolves itself at present, therefore, states Hirst, into the best means of recognizing the disease early. He calls attention to Schiller's test with the use of Hinselmann's colposcope as an important aid to an early diagnosis. The colposcope may be replaced by the more economical and portable binoculars with spectacle attachment. In the treatment of cervical cancer the high mortality of the radical operation, the negligible mortality of radium application, the approximate equality of results, the shorter hospitalization, the absence of suffering, the palliation of symptoms, and the fact that radium alone can be considered in advanced cases have relegated surgery to a subordinate place, although it cannot be ignored. The operation is as difficult as any in surgery and has a mortality of 16 per

cent in the hands of expert surgeons. Wertheim himself in the first 1000 of his 1500 operations had a mortality of 16%, as did Bonney in his first 227. Although both reduced their mortality to 9%, few could hope to rival them. The advantage of the radical operation lies in the removal of the regional pelvic glands, 21% of which were cancerous in Wertheim's statistics, 43% in Bonney's and 50% in Heyman's. The advocates of radium treatment are in the great majority. Almost all the prominent gynecologic clinics of the world have deliberately turned from surgery in cancer of the cervix to radium. A hopeful sign is that the operability of cervical cancers is increasing and the rate of cure has risen from 17% to over 28% in the past 5-year period.

**Radiotherapy.**—In Fukuoka, Japan, the IKEDAS (*Zentralbl. f. Gynäk.*, 1933, 57, 1651) have treated with radium 620 cases of carcinoma of the cervix between the years 1914 and 1927. These cases represent slightly less than one-half of the cases seen, the others being too far advanced to permit of radiotherapy. There were 238 cases in the operable group with 5-year cures in 151 (63.45%). In Group 2 (borderline cases), there were 79 cases with 5-year cures in 60 (75.95%). In Group 3 (inoperable cases), there were cures in 41 of 248 cases (16.53%), while in Group 4 (incurable cases), in spite of their apparently utterly hopeless condition, cures were obtained in 3 of 55 cases (5.45%). Taking the entire group of 620 cases, healing for from 5 to 18 years (personally observed) was obtained in 255 cases (41.13%). Of the cases which had recurrences, the most frequent sites were the local and parametrial tissues and then the inguinal, iliac and mesenteric glands. In 4 cases, recurrences occurred in glands of the neck. In 8 cases, the carcinoma was complicated by myomata, and in 2 by ovarian cysts. Radiotherapy had a good influence on the myomata, stopping bleeding and causing atrophy of the tumor, but had no effect on the ovarian cysts. There were 13 cases in which the carcinoma was associated with pregnancy. Of 6 cases which were in the second half of pregnancy, 5 gave birth to children which have developed normally for from 5 to 18 years, while in 1 case there was a stillbirth. When the associated pregnancy is in the first half of gestation, there is a greater tendency to abortion following irradiation, since of the 7 cases in this series, all terminated their pregnancies after radium treatment.

In considering the value of a mode of treatment, WARD (*Surg., Gynec. and Obst.*, 1933, 57, 546) emphasizes the essential differences between cancer of the cervix and cancer of the uterine fundus. In about 10% of cases, cancer originates in the cavity of the uterus, usually as adenocarcinoma. Cancer of the fundus is more frequent after the menopause, the mean age incidence being 8 years more than in cancer of the cervix. The ordinary panhysterectomy gives an average cure rate of 60% in these cases, and is, therefore, the method of choice; but unfortunately on account of obesity, senility, cardiovascular disease and diabetes, many of these patients are poor surgical risks, so that we must resort to intrauterine radium therapy and Roentgen ray, which give a cure rate closely approaching surgery. He believes that in these patients the ideal method is to combine radiotherapy and surgery when possible. In carcinoma of the cervix, all authorities agree that surgery is of little avail unless the radical operation of the Wertheim

or Schauta type is employed, which can be done only in operable cases. For the inoperable class, which includes more than 50% of those seeking relief, surgery has nothing to offer. Ward believes that in competent hands radium therapy combined with high-voltage Roentgen ray therapy gives results in advanced cases which are fully equal to the results obtained by surgery in operable cases, the primary mortality rate being less than 2% as compared to the 8 to 17% mortality of radical surgery. For the inoperable cases, radium therapy gives an average 5-year cure rate of 12 to 18% and has in the majority of cases a definite value in the palliation and prolongation of life. A 5-year cure rate of approximately 25% may be obtained in carcinoma of the cervix by either radical surgery or radium therapy in all those applying for relief. In the early cases, in which the disease is limited to the cervix, a 50% 5-year cure rate may be expected. The radical Wertheim operation requires skill and experience to be properly performed, and it must not be confused with the usual operation of complete or panhysterectomy which is frequently done for cancer of the cervix. The difference between an ordinary hysterectomy and the radical operation may be readily understood when compared to a simple mastectomy or the modern radical operation for cancer of the breast. He states that simple hysterectomy for carcinoma of the cervix is followed by fatal recurrence in nearly 100% of the cases. The safe use of radium, however, requires judgment and experience. A thorough understanding of its action and an appreciation of the complexities of its safe and efficient application is necessary. If a correct dosage and filtration is used, the cancer cells will be destroyed, but *not* the normal tissues. If too great a dosage and insufficient filtration is employed, the normal structures will also be destroyed, producing extensive necrosis, septic absorption, hemorrhages, fistulas and perhaps death. If too small a dosage is used, there will be a failure to destroy all the cancer cells. The foregoing statements of Ward, coming from one who is well qualified to handle these cases either from the surgical or the radiotherapeutic angle, are of special interest as they reflect the present thoughts on this subject in the Woman's Hospital in New York, where the results of treatment of cancer of the cervix are probably as good as in any institution in this country, or in the world.

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**Prognostic Value of Histologic Grading.**—Much has been written in the past decade concerning the prognostic value of the histologic pictures of the growth to be treated. From recent reports the enthusiasm which greeted such opinions when they were originally presented is not warranted. MALIPHANT (*J. Obst. and Gynec. Brit. Emp.*, 1933, 40, 444) studied the relation between cellular structure and response to radium treatment in a series of 236 cases of cancer of the uterine cervix, the growths being divided histologically into solid and glandular forms, with a subdivision of the former into three groups according to the predominant type of cancer cell. Of these growths, 4.2% were adenocarcinomas, and of the remainder 30.9% were spindle-cell cancers, 55.8% were transitional-cell cancers and 13.3% were spindle-cell cancers. Only 21% of the growths presented pure cell forms; in the remainder the grouping was based on the predominant type of cell present. The best immediate response to treatment was seen in the

spindle-cell cancers. The radiosensitiveness of the different histologic forms of cancer of the cervix is still unsettled, but the results of this investigation support to some extent the biologic relation between anaplasia and radiosensitivity. Though the spindle-cell cancers showed the best immediate results, the cellular type of the growth seemed to make but little difference so far as results were concerned. This may be accounted for by the balancing of the two factors of the malignant condition and radiosensitivity in the 4 histologic groups. Though the results in the 4 groups are practically equal, there are small differences which are noteworthy, since the results obtained in the group of adenocarcinomas were a little better than they were in the epidermoid cancers. The results in the solid carcinomas improved slightly with the degree of anaplasia of the tumor. He concludes from his study that, though the cytologic examination of the tumor would have supplied some information with regard to its immediate response to radium irradiation, it would not have been of any assistance in arriving at an ultimate prognosis.

A similar opinion has been expressed by JORSTAD and AUER (*Surg., Gynec. and Obst.*, 1933, 57, 583), working in the Barnard Free Skin and Cancer Hospital, St. Louis. From an analysis of the grading of all the cancers of the cervix treated by radium from 1917 to 1927 in the above hospital, they conclude that grading alone is of no prognostic value. However, they state that grading may be of great value in the radium treatment of these tumors, since the cases in Grades 1 and 2, which show more differentiation of cells, are much more radioresistant than the cases in Grades 3 and 4, which show more immature cells, so that, while the latter grades are more malignant, they are more responsive to radium irradiation. Grading may be the deciding factor in the decision to employ surgical treatment rather than radium therapy.

**Injuries to Urinary Organs by Irradiation.**—That radium irradiation has definite potentialities for harm which are not always appreciated by the inexperienced is shown by Dean's (*J. Urol.*, 1933, 29, 559) report calling attention to the delayed radium burn of the urinary bladder. In his series of 47 cases, this caused symptoms in from 10 to 114 months after the radium treatment had been given. The lesion is really the result of an obliterative endarteritis and consists of a white avascular central area surrounded by a zone of dilated bloodvessels. In some cases the center breaks down and forms an ulcer. The onset of symptoms, though characteristically long delayed, is usually sudden and consists of frequency, dysuria and hematuria with severe pain. At times the hemorrhage is severe enough to threaten life. The diagnosis is easy if the possibility of the condition is kept in mind and is based on the history of previous irradiation and the local findings by cystoscopy. Biopsy may be necessary as the picture may closely simulate carcinoma. The ulcers which are present in two-thirds of the cases are located in the posterior third of the base of the bladder, almost in the midline. Before ulceration occurs the prognosis is good, but when ulceration is extensive the prognosis must be guarded. The prophylaxis of the lesion is the use of the minimal amount of irradiation necessary for cure and proper shielding of the bladder. The treatment of the developed lesion is the relief of pain and treatment of the infection.

Pain may usually be relieved by teaspoonful doses of tincture of hyoseyamus, every 4 hours, and occasionally the use of codein. Heat and rest are important and lavage of the bladder with 1 or 2% of phosphoric acid is of use. The phosphoric acid may be increased gradually to a 5% strength as the bladder becomes more tolerant and treatments are given at increasing intervals until healing is complete, which may take many months. Another type of radium injury, though not so common, reported by COUNSELLER (*Proc. Staff Meet. Mayo Clinic*, 1933, 8, 533) is the formation of an enterovaginal fistula following the application of radium to the cervical stump. In this case, 7 years after subtotal hysterectomy for fibroids, a yellowish-brown discharge from the vagina was noted. A year later, with the diagnosis of carcinoma of the cervical stump, radium was applied for 12 hours. Within 3 months a vaginal intestinal fistula had developed which did not close during the following 2 years. Operation was then undertaken, and when the abdomen was opened it was found that the ileum was attached to the vagina about 60 cm. from the ileocecal valve, and at this point there was a fistula into the vagina just under the cervical stump. There were no other adhesions or evidences of remaining malignancy in the pelvis, and separation of the bowel and closure of the fistula was successfully accomplished. He believes that the fistula in this case was undoubtedly due to the fact that a loop of small bowel became adherent to the vagina following hysterectomy 7 years prior to the development of the carcinoma in the stump rather than because radium had been misapplied. About 100 cases of cancer of the cervical stump have been observed at the Mayo Clinic, and it is the custom to treat these lesions with radium.

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**Results of Surgical Treatment.**—In the report of SCHILLING (*Zentralbl. f. Gynäk.*, 1933, 57, 2422) from the gynecologic department of the University of Leipsic, under the direction of Stoeckel, there were 465 cancers of the cervix treated between 1923 and 1926. The Wertheim operation was performed on 35, of whom 11 (31%) were free from recurrence after 5 years and the primary mortality was 20%. Most patients were irradiated with radium before operation, and all had had postoperative Roentgen ray treatment. In 150 cases the radical vaginal hysterectomy of Schauta (Stoeckel modification) was done, of whom 87 were free from disease 5 years later (58%) and the primary mortality was 4%. In 287 patients, irradiation alone was employed, of whom 59 (20%) were free from disease for 5 years or longer and the primary mortality was 1.4%, being due to embolism, sepsis, peritonitis or heart disease. The dosage of radium was between 2000 and 4000 mg. hours, given in a short time and usually supplemented later by deep Roentgen ray therapy of from 95 to 110% erythema dose. Classifying the cases by the degree of involvement, irrespective of the method of treatment employed, it is shown that Group 1 contained 126 cases, with 46% cures; Group 2, 119 cases, with 43% cures; Group 3, 154 cases, with 18% cures; and Group 4, 60 cases, with 15% cures. In 8 cases the cancer was complicated by pregnancy, and of these 3 remained free from recurrence over 5 years. From the above statistics it may be readily seen that the best results in this clinic have been obtained by the use of the radical vaginal hysterectomy, with a

mortality rate so low as to fully justify the continuation of such treatment in the trained hands which make up the personnel of that organization. There are, however, not many clinics which can approach a 5-year cure rate of 58% from this operation.

**Operation Combined With Irradiation.**—In order to get the maximum effect from irradiation, two methods have been presented in which the operation is performed and irradiation is directly applied to the carcinomatous growth. In the first method, described by CURTIS (*Am. J. Obst. and Gynec.*, 1933, 26, 569), the necrotic cervical growth is treated with surgical diathermy or prophylactic radiation at least 3 weeks prior to operation. Preliminary deep Roentgen ray therapy may serve equally well in healing the sloughing cancerous surface. When the surface has become free from necrosis and infection, a pelvic examination is made under anesthesia to determine the extent of the growth and the amount of intervention required, and surgical exposure of the cancer-bearing uterus and adjacent cellular tissues is undertaken. With blunt dissection the bladder is mobilized upward, the cervix being encircled with an incision as in making a radical vaginal hysterectomy, and the vaginal mucosa is painstakingly dissected laterally and posteriorly, along natural lines of cleavage. The body of the uterus and the regions of the broad ligaments and cardinal ligaments are now well visualized. With the organ half delivered broadside, vaginally, the bladder safely anchored in its elevated position with a catgut suture holding it high on the uterus, and the paracervical tissue exposed, a massive radium treatment is possible. Radium needles or radon seeds are now inserted where needed, near to or into the cervix or far from it, as indicated, with assurance of safety of the adjacent vulnerable organs. Although the ureters are subject to possible injury, they are considerably retracted incident to the dissection and displacement of the bladder and are relatively immune. Preliminary ureteral catheterization may merit consideration in selected cases, but Curtis has not resorted to it. Injury of a uterine artery is a possibility, but he has not seen that complication despite many years' custom of introducing radium needles into the cervical parametrium. Palpation of the artery preliminary to burying a radium needle in its vicinity appears unnecessary. After burying the radium needles, as described, a chain tandem of radium capsules is inserted into the uterine canal in the usual manner and a vaginal pack completes the procedure. The above method of treatment is advocated for cases in Group 2 or to the less advanced cases in Group 3 in which there is some hope of cure.

In the second method of operation combined with direct irradiation, described by SCHUMANN (*Am. J. Obst. and Gynec.*, 1933, 26, 260), advanced cases of pelvic carcinoma are attacked by applying Roentgen rays directly to the affected tissues without the intervention of the abdominal parietes. The procedure is carried out in connection with the implantation of radium in the cervix or the uterine cavity, as the case may require, and has only been applied in instances where the entire pelvis is a mass of carcinomatous tissue, with extension into the adjoining lymph nodes. The technique of this procedure consists in placing the patient in the lithotomy position for the performance of a



biopsy and the application of 50 mg. radium to the cervix or uterine cavity. The patient is then placed in the Trendelenburg position and a median abdominal incision is made about 6 to 8 inches in length, and the abdominal walls are widely retracted by means of a Balfour retractor. The intestines are carefully walled off with a large gauze pad, after which the abdominal wall and all the pelvic tissues except those involved in the malignant growth are protected from irradiation by being covered with sheet lead, 2 mm. in thickness. A roll of such sheet lead and a large heavy scissors are in readiness, having been sterilized by boiling. Strips of lead are cut to fit the interior of the abdomen and are then snugly molded into position (with the fingers) so as to isolate the tumor area absolutely, all other tissues being covered by strips of lead. A large sterile dressing is then applied, and the patient transported to the Roentgen ray room, where she is given a full therapeutic dose of Roentgen ray irradiation, *i. e.*, 150 ma., 18-inch distance, 130 kv., 6 mm. aluminum filtration. Upon the completion of the treatment the sterile dressing is replaced, the patient is wheeled back to the operating room, the lead and gauze packs are removed and the incision is closed. No attempt is made to remove any of the malignant tissues. The operation is much facilitated when a light and simple operating table is used and avertin is the anesthesia of choice, because the patient lies quietly asleep during the entire procedure and time is not a particular factor.

**Pelvic Sympathectomy for Pain.**—In cases of inoperable carcinoma of the cervix, where the patient suffers from constant pain, the operation of pelvic sympathectomy has been successfully employed in several clinics both in this country as well as abroad, where the procedure was first advocated. CORRE (*Zentralbl. f. Gynäk.*, 1933, 57, 72, 77), of Lyon, has resected the presacral nerve in over 200 cases with results that appear to be very satisfactory, although in the majority of his cases the pain was due to other conditions than malignant disease. He has never had any bad results which could be attributed to the operation, such as bladder disturbances or secondary trophic changes in the vagina or vulva, though since his first operation was performed more than 7 years ago, ample time has elapsed for these changes to appear. The largest series that has been reported in this country is that of GREENHILL and SCHMITZ (*J. Am. Med. Assn.*, 1933, 101, 26), who have performed the operation on 13 patients with inoperable carcinoma of the cervix. They removed portions of the presacral nerve (superior hypogastric plexus), varying in length from 5 to 10 cm., making certain that nerve tissue was present by microscopic examination. They regarded the results as most satisfactory because all of the 11 patients who survived the operation experienced relief from pain. Three women had temporary diarrhea for a few days after the operation and 3 women developed paresthesia in the back of the thigh and popliteal space, but no bladder disturbances were observed. Two patients died, both on the 25th day after operation, 1 from cachexia and the other from bronchopneumonia and cachexia, but both were entirely relieved of their pain. They comment upon the fact that the term "presacral nerve" is a misnomer and apt to be confusing since the structures to be removed are prelumbar rather than presacral and also

are arranged in the form of a plexus rather than as a single nerve. The term superior hypogastric plexus is more accurate. The technique of this operation is not complicated and well within the field of the gynecologic surgeon, as opposed to the operation of cordotomy, which has more dangerous possibilities and belongs entirely within the field of the neurosurgeon. This operation has been performed by BEHNEY (*Am. J. Obst. and Gynec.*, 1933, 25, 687) on 7 patients who were in extreme pain from Stage 4 carcinoma of the cervix. Complete and permanent relief of pain in the lower abdomen and thighs was secured in 5 patients, while in 2 cases the operation failed to give relief. All incisions healed by first intention and there were no postoperative complications. In spite of the extensive involvement of the bowel with metastatic carcinoma, the slight amount of distention and gas pains was a striking feature. In fairness to the operation, Behney states that in 1 of the cases which failed to get relief, the omentum was so densely adherent to the iliac vessels that exposure of the sympathetic plexuses was impossible, while in the other unrelieved case he feels that he failed to include all of the afferent fibers in the tissue which he removed. In other words, relief cannot be expected from a nerve resection of this type unless all of the afferent fibers are interrupted. Another enthusiastic report of this operation has been presented by WETHERELL (*J. Am. Med. Assn.*, 1933, 101, 1295), who presents his experiences in 7 cases, only 2 of which were cases of pain due to inoperable cervical cancer. He believes that the operation is entirely safe and well worth while when pain can no longer be relieved by medication. (Sympathectomy is not uniformly successful, but, as Behney has stressed, it is a valuable operation in certain carefully selected cases. C. C. N.)

## DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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## MYCOTIC INFECTIONS OF THE SKIN.

A RÉSUMÉ OF CURRENT CONCEPTION.

By JOHN H. STOKES.

THE range of literature covered in this summary includes certain of the basic contributions as far back as 1929, but the larger part of the material is drawn from the years 1931 to 1933.

Mycotic infections comprise approximately 10% of the general clientele of dermatologic clinics. GOODMAN (*Arch. Dermat. and Syph.*, 1931, 23, 872) pointed out the inverse relation between eczema and mycotic infections, which is characteristic of the diagnostic trend of

the times; eczema decreasing in frequency from 25% in 1925 to 11% in 1929, while mycotic infection increased from 3% in 1925 to 10% in 1929. For European clinics the experience of SCHMIDT (*Arch. f. Dermat. u. Syph.*, 1933, 169, 259) is fairly typical. Mycotic infections constitute 10% of the patient material, and 50% of these mycotic infections involve the hands and feet. There has been a gradual increase in the incidence of this group of diseases in the last several years. Groups of students studied in widely separated parts of this country are represented by the reports of LEGGE, BONAR and TEMPLETON (*Arch. Dermat. and Syph.*, 1933, 27, 12) and MUSKATBLIT (*New York State Med. J.*, 1933, 33, 632). These authors give figures ranging from 50 to 89% of men showing clinical evidence of infection and 15 to 17% of women. The first-named authors attribute the sex variation to difference in gymnasium conditions and point out the increase from 51 to 78% in the men during a semester of gymnasium work. Weidman, in discussion, however, stated that the opposite conditions obtained in his studies and attributed the difference to sex and susceptibility. In CREMER's report (*Arch. f. Dermat. u. Syph.*, 1933, 169, 244) on Amsterdam conditions found 84% of students had clinically suspicious lesions.

The reported incidence varies greatly with the criteria employed for diagnosis. The presence clinically of fissuring and eczematoid eruptions between the toes is the source of the high figures mentioned. When culture is employed, however, as the most authentic diagnostic criterion, the proportion of positives varies widely, depending presumably upon expertness in laboratory facilities, from 14% in Cremer's series, just mentioned, and 17.9 per cent in that of Muskatblit, to the higher proportions of positive cultures obtained in those cases in which it was possible microscopically to demonstrate the fungus in scales, as, for example, Muskatblit's 50.8% and a variety of figures cited by Schmidt ranging from 30 to 85%. The striking difference between the cultural results on hands and feet is illustrated by Schmidt's 23.4% positive cultures on the hands, as against 73% positive cultures on the feet. The difference is attributable to the absence of fungi in the so-called dermatophytid of the hands, as will presently be explained.

**Pathogenesis—Dermatophytoses and Dermatophytids.**—The conception of the "id" extended from the field of eutaneous tuberculosis by Jadassohn and Guth is one of the most important recent aspects of dermatomycology. In accordance with this conception, no inconsiderable part of the visible eruption of a dermatophytosis is a secondary sensitization phenomenon or dermatophytid in which no fungi are present—a dermatitis attributable to toxic or allergic reaction, from a primary focus sometimes distinguished with difficulty clinically from the general eczematous picture presented by the patient. A large proportion of the primary foci, or dermatophytoses proper, in which the fungi are present, are situated upon the feet, in the flexures of the groin, the anogenital cleft, and similar situations suitable for the growth of the fungus, while the secondary sensitization eczema and other "id" manifestations may be found upon the ears, the face, the palmar and dorsal surfaces of the hands and in the form of more or less widely distributed dermatitic eruptions on the trunk and lower extremities. In addition to the eczematoid dermatophytids, an important and

interesting group of "id" manifestations includes toxic erythemas, sometimes scarlatiniform, exfoliative and universal in distribution; erythema multiforme-like eruptions, presumably due to the distribution of the fungi *via* the blood stream and their fulminating destruction in the hyperallergic skin; and including even extensive bullous and hemorrhagic eruptions. The clinical pictures long classified as pompholyx of the hands and dyshidrosis, in which, according to the views of the German and Swiss school, the causative fungus is absent in the overwhelming proportion of cases, are dermatophytids. An interesting controversy over the presence of the fungus in these lesions of the hands has developed over the American championship of the so-called "mosaic form," described by MACKEE, WEIDMAN and others, but interpreted by Continental observers largely as artefact (BECKER and RITCHIE, *Arch. Dermat. and Syph.*, 1930, 22, 790; JADASSOHN and PECK, *Arch. f. Dermat. u. Syph.*, 1929, 158, 16; CREMER, *Ibid.*, 1933, 169, 244).

It is important to realize that the secondary mycotic eruptions ("ids") may not only give rise to confusing pictures of eczema, erythema multiforme, toxic erythema and exfoliative dermatitis, but that they may be accompanied by constitutional symptoms, most frequently observed in connection with the granulomatous mycosis called *kerion Celsi*, a macaroon-like fungating tumor of the scalp, and including headaches, vomiting, anorexia, fever, marked regional adenopathy and leukocytosis.

MUENDE (*Post-Grad. Med.*, 1933, 9, 197) summarizes the current conception of the sensitization mechanism involved in the production of the "phytid" by stating that fungous elements are thought to enter the blood stream and sensitize the skin and that later, at the height of development of the primary focus, showers of spores enter the blood stream, are destroyed in the skin to which they are distributed, giving rise to "ids" with various degrees of intensity of local reaction. The toxin of mycotic organisms, spoken of generically as trichophytin, also probably plays a part in this picture.

The range of clinical appearance of dermatophytids may be inferred from Muende's list—lichenoid follicular trichophytid in grouped arrangement; mycotic lichen spinulosus, corymbiform eruptions, annular eruptions, eczematoïd and psoriasiform lichenoid eruptions, the dyshidrotic and pompholyx forms on the hand, scarlatiniform eruptions, desquamative postscarlatiniform pictures on the palms and soles, urticarial and erythema multiforme-like eruptions and erythema nodosum.

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**The Dermatophytoses.**—While the most characteristic localization for these lesions containing the fungi is, of course, the hands and feet, particularly the interdigital spaces of the feet, primary foci may appear also at the anus, in the gluteal cleft, in the axillæ and the inguinal folds. SCHMIDT (*Arch. f. Dermat. u. Syph.*, 1933, 169, 259) well illustrates the range in clinical appearance embraced in the modern classification of dermatophytoses of the hands and feet. He described 10 eruptions of the hands, due to epidermophytes, including interdigital erosions; the pseudodyshidrotic *epidermophyte* which produces vesicles along the contact surfaces of the fingers and on the backs of the fingers

and hands; a dry scaly type with impetiginous borders; localized eczematoid and fissured epidermophytosis of the palms and fingers; a dry squamous and fissured modification of the same type; grouped hyperkeratotic eczematous lesions of the fingers; eczematoid and fissured eruptions of the finger webs and knuckles; circumscribed, plaque-like, circinate and annular lesions of the backs of the hands and epidermophytosis with superposed dermatitis.

**Moniliases and Oidiomycoses.**—This large group of yeast-like fungi has grown greatly in importance under recent investigative work. While yeasts can be grown from all parts of the skin and most of them are not pathogenic, BENHAM and HOPKINS (*Arch. Dermat. and Syph.*, 1933, 27, 532) seem to have been able to single out *Monilia albicans* as the probable pathogen in the yeast-like dermatoses. This fungus was not obtained from the skin of 100 normal young adults, while other yeast-like organisms were obtained in 72%. On the other hand, the *Monilia albicans* is a well-recognized pathogen associated with a number of cutaneous pictures, including, in accordance with HOPKINS (*Arch. Dermat. and Syph.*, 1932, 25, 599) detailed summary, *crissio interdigitalis*; paronychia of sporadic and epidemic types (the latter in fruit canners, Kingery and Chienes); *perlèche* (Finnerud, and Robinson and Moss); intertrigo in the distribution of *tinea cruris* and also under the breast, at the umbilicus and in the intergluteal and perianal folds. Additional monilia lesions of the skin include vulvitis (Guilini, Kehrer, Ferichs, Bloch and others), both of non-diabetic and diabetic types; a rare form of intertrigo of the toes (Weidman, Robinson and Moss); oral and cutaneous thrush in infants and children; moniliasis of the diaper region; moniliasis after continuous baths and wet dressings; moniliasis of the tongue; moniliasis of the vagina; balanoposthitis; non-intertriginous dermatitic moniliasis of the forearms, nipples and tips of the fingers. Four of the most important and interesting groups of yeast infections of the skin as currently conceived include the well-known seborrheic eczema and seborrheic dermatitis, the so-called *cryptococcosis epidermica* and the moniliatids or *levurids*. Under seborrheic eczema should be mentioned the debated conceptions of Benedek, in which the cutaneous eruption is regarded merely as an outcropping of a general systemic infection with *schizosaccharomyces hominis*; the autoinoculable "seborrheic eczema" due to *cryptococci* (Cleveland White); and the form of seborrheic dermatitis associated with the presence of the *Microsporon of Mallassez* (MacLeod and Dowling), involving particularly scalp, neck and face. *Cryptococcosis epidermica* is a patchy, vesicosquamous eruption, widely scattered over the trunk and extremities and frequently with a predilection for seborrheic areas. It has been particularly discussed in the American literature by C. J. White and Schwartz. The group of moniliatids investigated principally by RAVAUT and RABEAU (*Presse méd.*, 1932, 40, 1925) includes a group of mycotic intertriginous eruptions involving the inframammary and retroauricular folds and the umbilical region. The mycotic phase of this condition is the intertriginous eruption and associated with it may be found so-called eczematiform parakeratoses which are dry squamous dermatitic eruptions associated with secondary sensitization to the yeast fungi in the primary foci. Some interest

attaches to the frequency with which monilia appears in the gastro-intestinal tracts of patients with moniliform eruptions and also psoriasis, the suggestion being made that the intestinal focus contributes materially to the general sensitization responsible for the cutaneous manifestation.

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**Fungous-pyogenic Interrelations.**—Much interest attaches to this group of cutaneous lesions, of which the chief clinical examples are the dermatophytosis-like eruptions of the hands from which no fungi can be obtained. These include especially dermatophytids, such as keratolysis exfoliativa, acrodermatitis perstans, amycotic eruptions of the hands and feet (Mitchell) and resistant pseudomycotic eruption of the feet (Andrews). In this group should be included also the so-called psoriasis pustulosa (Barber). This important group of troublesome and diagnostically confusable eruptions, distinguished either by their sterility to all culture methods or the impossibility of cultivating fungi from them, are in many cases clinically indistinguishable from typical culturally proved mycoses of the affected region. The studies of Ravaut and Rabeau have pointed to the presence of streptococcal complications in the so-called "levurid," in that bacterial organisms in cultures from the intertriginous "levurid" lesions, including several types of streptococci, may give rise to typical allergic and sensitization responses on intradermal injection.

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**Fungous-allergic Interrelations.**—Several recent publications, including a paper by WHITE and TAUB (*J. Am. Med. Assn.*, 1932, 98, 524) have directed attention to the predisposing effect of superficial fungus infections in inducing allergic dermatitis in susceptible persons. White cites a number of cases in which the preceding mycotic infection of the hands apparently prepared the way for allergic response to contact irritants, including cottonseed oil, oatmeal, buckwheat. This conception of interrelation between allergic manifestations and infections has, of course, been well recognized in the field of asthma and other allergic diseases.

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**Diagnosis of Mycotic Infections—Trichophytin Test.**—PECK (*Discussion, Arch. Dermat. and Syph.*, 1932, 25, 1118) has well summarized the process of diagnosing a cutaneous mycotic infection: "(1) In order to make a positive diagnosis instead of a presumptive one of fungus infection, the fungi, of course, must be demonstrated. The fungi should be found in the primary lesion and not in the trichophytids in the average case. The most difficult thing in a case of this kind is to make up one's mind where to look for the fungi, as it is almost impossible to determine where the epidermophytosis ends and the epidermophytids begin. Even in the primary lesions it is often possible to find the fungi only by culture. (See preceding summary.) (2) The trichophytin reaction should be strongly positive. While it is conceivable that there may be a positive anergy, it is not the rule. (3) A flaring up of the trichophytids even in the presence of a moderately positive trichophytin reaction is one of the best proofs for a diagnosis of epidermophytids. If one takes the casual dermatologic cases as they come into the clinic, in more than 50% a moderate degree

of hypersensitiveness to trichophytin is found; therefore, on a moderate reaction alone a diagnosis cannot be made. The control for the trichophytin must be used in the correct dilution to obviate pseudoreactions, and if the diluted trichophytin is allowed to stand too long it loses its potency." Peck has described a case of hemorrhagic trichophytids on the legs which developed after injections of trichophytin. Sulzberger pointed out that for adequate diagnostic testing oïdiomycin should be used as well as trichophytin, some patients reacting to only one and others to both. MUSKATBLIT and DIRECTOR (*Arch. Dermat. and Syph.*, 1933, 27, 739), in an extended review of the trichophytin test, point out that there is as yet no standardized and universally recognized preparation of trichophytin either for diagnostic or therapeutic purposes. The usual dose of the available commercial preparations is 0.1 cc. of the undiluted extract on the flexor surface of the forearm. In 48 hours a negative test shows only a red dot at the site of injection or a pinkish macule no larger than the primary wheal ("depot" reaction). A weak positive is an erythematous patch, 2 to 4 cm. in diameter, and a strong positive shows an infiltration of one large or several small papules, at times vesicular in character and at times with a bright red halo. A positive reaction reaches its height in 48 hours and disappears in 1 week. Delayed reactions, disappearing in 3 to 5 days, increasing reactions, developing in from 3 to 7 days, and persistent reactions, lasting sometimes for several weeks, have been noted.

In 300 microscopically and culturally proved cases, these authors obtained 60.3% positive trichophytin tests, the tests being in agreement with the clinical diagnosis in 65.4% and in disagreement in 34.6%. The trichophytin test more frequently corroborated the clinical diagnosis than did the laboratory findings; 72.3% of the cases proved mycotic by the laboratory gave positive trichophytin reactions. Highly inflammatory lesions gave a high percentage of positive tests.

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**Prevention of Fungous Infection of the Feet.**—The contributions of OSBORNE and HITCHCOCK (*J. Am. Med. Assn.*, 1931, 97, 453), on the use of sodium hypochlorite, and of GOULD (*Ibid.*, 1931, 96, 1300), on 10% sodium thiosulphate for the prevention of the transmission of mycotic infections of the feet in gymnasiums, shower baths and similar distributing centers for the dermatophytoses, deserves to be recalled. It is curious that the former authors noted sodium hypochlorite to have no treatment value in the concentration used, yet the preventive effect was so marked that no new cases of ringworm of the foot appeared in the Buffalo high schools after the trays, containing this solution, had been installed in the gymnasium showers. The sodium thiosulphate prophylaxis, proposed by Gould, is probably notably more expensive than that with sodium hypochlorite in large institutions.

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**Treatment of Fungous Infections.**—Fungicidal methods recently proposed include the use of formaldehyde vapor for the sterilization and saturation of the leather of shoes and gloves, as proposed by HENDERSON (*Arch. Dermat. and Syph.*, 1932, 26, 710). He points out that when shoes have been so treated during the night a distinct amelioration or disappearance of symptoms of mycotic infection on the feet begins the following day. The leather absorbs considerable amounts of the for-

maldehyd vapor. EMMONS (*Ibid.*, 1933, 15, 21) found iodine and chlorine (surgical solution of chlorinated soda) to have the highest phenol coefficient when tested against trichophyton and monilia suspensions. LEVINE (*J. Am. Med. Assn.*, 1933, 101, 2109) used phenyl mercuric nitrate in tinea and yeast infections of the skin in 262 cases, of which 205 were cured. An ointment of equal parts of wool fat and an aqueous solution of the chemical in the strength of 1 to 1250 or 1 to 150 by weight, with the addition of 10% glycerin applied twice a day, was found most satisfactory. TAYLOR (*J. Am. Pharm. Assn.*, 1933, 22, 410) found that the well-known effectiveness of potassium permanganate solution is probably due to the manganese rather than the permanganate element in the combination. Manganous sulphate, 1 to 1000, in water, gave much more striking results and 10% manganous oleate in anhydrous lanolin was also effective, but only when used on the foot. AYERS and ANDERSON (*J. Allergy*, 1933, 4, 146) pointed out the frequent intolerance of Whitfield ointment as a cause of failure in the treatment of dermatophytosis. BARKSDALE (*Med. J. and Rec.*, 1932, 136, 494) treated 80 negro children, on whom Roentgen ray could not be used, with 1% bismuth violet, 10% salicylic acid in 70% alcohol, using 1 to 2 coats of the dye applied daily without other dressing. The results were uniformly satisfactory, the patients being cleared of infection in 6 to 10 treatments.

The dangers of thallium epilation, when carried out under poorly controlled conditions in large institutions, is well illustrated by the appearance of several instances of poisonings, the worst example so far recorded being that of an orphan asylum in Granada, Spain, in which 14 children died (*Foreign Correspondence, J. Am. Med. Assn.*, 1933, 100, 678).

The status of trichophytin as a therapeutic measure for desensitization is still in process of evaluation. VAN DYCK, KINGSBURY, THRONE and MYERS (*New York State J. Med.*, 1932, 32, 1101) discuss in detail the technique of its administration and in a series of patients obtained cures in 30%, marked improvement in 33%, slight improvement in 32% and failure in 5%. SULZBERGER and WISE (*J. Am. Med. Assn.*, 1932, 99, 1759) lean toward conservatism and while reporting desensitization in 15 out of 18 cases studied, only two-thirds of the number seemed benefited by the treatment on the basis of long remission or marked improvement or apparent cure. These authors produced no serious reactions in 100 patients treated with trichophytin but warn of the possibility of producing intractable, generalized exfoliative dermatitis, generalized eczema or even shock and fever. OSBORNE, PUTNAM and RICKLOFF (*New York State J. Med.*, 1933, 33, 1270), after treating 100 cases of chronic relapsing ringworm infections of hands and feet with trichophytin, conclude that equally good results could have been obtained without trichophytin and that apparently good results later proved to be temporary. Furthermore these authors stress the importance of unfavorable reaction in the form of focal flare-ups, widespread dermatophytids, asthma and urticaria. The conclusion seems inevitably that the use of this agent is still in an experimental stage and its use requires great caution to avoid untoward reaction.



## PHYSIOLOGY

PROCEEDINGS OF  
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF FEBRUARY 19, 1934

**A Method for the Estimation of the Oxygen Content of One Cubic Millimeter of Blood.**—JOHN S. DONAL, JR. (Laboratory of Pharmacology and the Johnson Foundation for Medical Physics, University of Pennsylvania, Philadelphia). It has been observed (Donal, 1930) that the introduction of small amounts of a gas mixture containing oxygen into an evacuated space surrounding a heated tungsten filament results in the formation of positive ions at the filament surface. The ions so formed may be collected at a negatively charged electrode and the resulting current may be amplified and measured by means of a sensitive galvanometer. The galvanometer deflections have been found to be directly proportional to the amount of oxygen introduced into the filament chamber and independent, over a wide range, of the partial pressures of nitrogen and carbon dioxide in the gas mixture.

Samples of 1 cmm. of blood sealed in capillary glass tubes were extracted by breaking the tube in a high vacuum. The dried gases were then introduced into the filament chamber and the resulting galvanometer deflection compared with the deflection yielded by a sample of room air introduced in the same manner. The results of a series of such determinations were compared with the results of estimations made on large portions of the same samples of blood by the method of Van Slyke and Neill. After correction for a systematic error of +0.16 volumes per cent the average difference between the results of 88 consecutive estimations and the values given by the Van Slyke method was 0.56 volumes per cent and the maximum difference encountered was 1.9 volumes per cent.

**Oxygen Absorption Through the Skin.**—SAMUEL GOLDSCHMIDT, BARTGIS MCGLONE and JOHN S. DONAL, JR. (Laboratories of Physiology and Eldridge R. Johnson Foundation, University of Pennsylvania). The following observations constitute convincing evidence that oxygen may penetrate the skin of the forearm, at least into the blood of the cutaneous vessels.

When the circulation is partially or completely occluded:

1. The normal color of the skin is maintained when the arm, in an atmosphere of oxygen, contains its usual amount of blood. The cyanosis which usually develops on the skin of an arm in air with arrested or impeded circulation is not in evidence except on some portions of the hand when the arm is in an atmosphere of oxygen.

2. The skin of the forearm, congested with blood, in oxygen is pink, in contrast to the bluish or dusky color of an arm in air, nitrogen or hydrogen under like conditions.

3. Under the above experimental conditions the skin color may be altered from normal to cyanotic or from pink to blue or *vice versa* by changing the gaseous atmosphere appropriately.

4. The oxygen content of the cutaneous blood of a forearm, in an atmosphere of oxygen, is invariably higher than it is when the arm is in nitrogen.

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**The Participation of the Neuroglia in Myelin Formation in the Prenatal Human Brain.**—BERNARD J. ALPERS, and WEBB HAYMAKER (Institute of Neurology, Pennsylvania Hospital). It is desirable to know the histologic elements concerned in myelin deposit in the brain. For this reason the brains of human fetuses ranging in age from 5 to 9 months were studied by silver methods for all forms of neuroglia and microglia and by methods for neutral fat, osmic acid fat and myelin. It was found that all the elements, astrocytes, oligodendroglia and microglia contain neutral fat from the fifth month on. Osmic acid fat is found only in the seventh and eighth stages. Myelin appears suddenly in the ninth month, but is not demonstrated before. Neutral fat is present in the bloodvessel endothelium in the fifth month.

The astrocytes are active in the myelinization process. Fat of all types is found in their cytoplasm at various stages. Myelin is found in the ninth month in the nerve cells and in the astrocytes. Furthermore, there seems to be a symbiotic relationship between the processes of the astrocytes and those of the nerve cells in the process of myelin deposit. These cells, therefore, play an important rôle in myelin deposit.

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**Potentials Produced in the Spinal Cord in Response to One and Two Stimuli.**—JOSEPH F. HUGHES and HERBERT S. GASSER (Laboratory of Physiology, Cornell Medical College). Following stimulation of a dorsal root of a cat by a single induction shock there are set up in the spinal cord electrical potential changes, the complexity, form, and duration of which depend upon the experimental conditions obtaining at the time of the experiment. In deep ether narcosis the form of these potentials as recorded by the cathode ray oscillograph technique, when one lead is placed on the dorsal surface of the cord at the root level and the other several centimeters above, shows a period when the lead at the root level is negative followed by one in which it is positive to the more distal one. In light ether anesthesia additional negative crests make their appearance. The transition from the decerebrate to the spinal state is accompanied by an increase in the number and depth of these crests.

The magnitude of these potentials is greatest at the root level and falls off rapidly above and below it corresponding to the area of distribution of the collaterals of the primary neurone. Simultaneous stimulation of two adjacent homolateral roots gives evidence that the potentials are generated beyond a point where the two roots overlap. Antidromic stimulation of the motor horn cells through the sciatic nerve failed to affect the development of the cord potentials (as seen in leads from the dorsal surface of the cord) following stimulation of a dorsal root.

Recovery of the cord potentials after previous activity as studied through stimulation of the primary neurone did not begin until after

10 $\sigma$  had elapsed. Complete recovery did not occur until the electrical activity set up by the first stimulus had subsided, a time varying from 100 $\sigma$  to more than 880 $\sigma$ .

Comparison of the course of the cord potentials in response to a small conditioning and a large testing shock, with the size of the homolateral flexor reflex, shows that the cord potentials present a sufficiently typical background to enable one to predict the type of myographic response to the testing shock. The transition from reflex facilitation to "inhibition" has been shown to be accompanied by a transition in the form of the cord potentials. A negative wave with poorly developed crests followed by undeveloped positive wave goes with reflex facilitation while a negative wave with prominent crests and a well developed positive wave goes with reflex inhibition. The development and release from reflex inhibition are related to the mode of elimination and recovery of the late crests in the first negative complex of the cord potentials and can be explained largely on the basis of failure of excitation to reach the motor horn cells due to the interposition of refractory inter-nuncial neurones.

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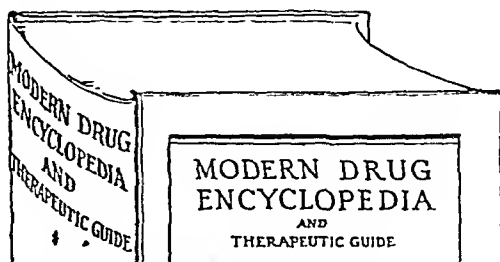
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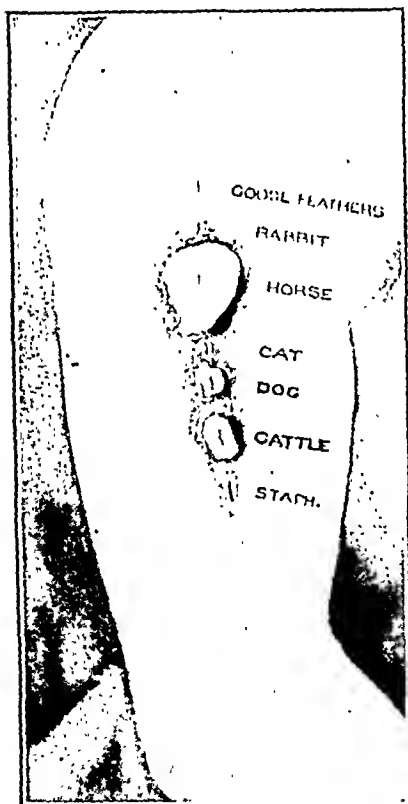
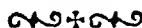
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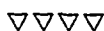
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Medical Director, Russell Sage Institute of Path-  
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*Third edition, thoroughly revised, published 1934. Octavo, 668 pages, illustrated  
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THE FIRST TWO EDITIONS OF THIS WORK were exhausted with unusual rapidity. The extensive changes necessitated by recent progress have made necessary a thorough revision for this third edition. Among the sections that have been added or altered are: Prerenal azotemia, hypochloremia, the xylose test, the volume of the glomerular filtrate, albuminuria due to cerebral lesions, salyrgan, the capillaries and veins in hypertension, the therapeutic use of magnesium sulphate, the treatment of mercury poisoning, the kidney in multiple myeloma, the injection of acacia in edema, renal lesions accompanying various forms of endocarditis, skeletal changes in renal disease, arteriolar necrosis in hypertension, the relations of the pituitary gland and basophilic adenoma to hypertension, hypertension due to bulbar lesions, allergy and hypertension, electrocardiographic changes with hypertension, the cerebrospinal fluid in hypertension, and the nature and treatment of renal and hypertensive disease in pregnancy. The differentiation of renal and extrarenal factors in the production of various azotemias, so important for rational treatment, has been stressed throughout the book.

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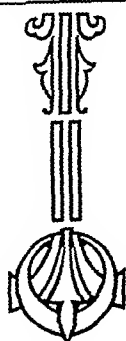
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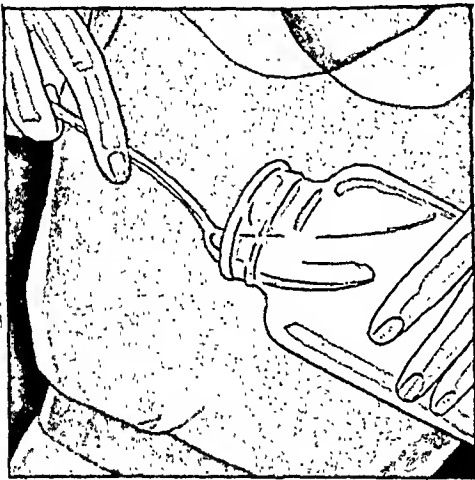
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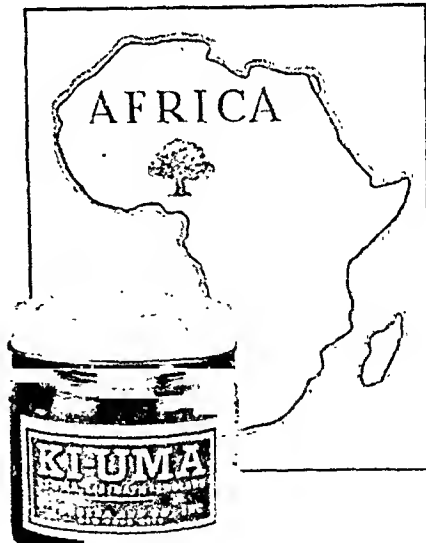
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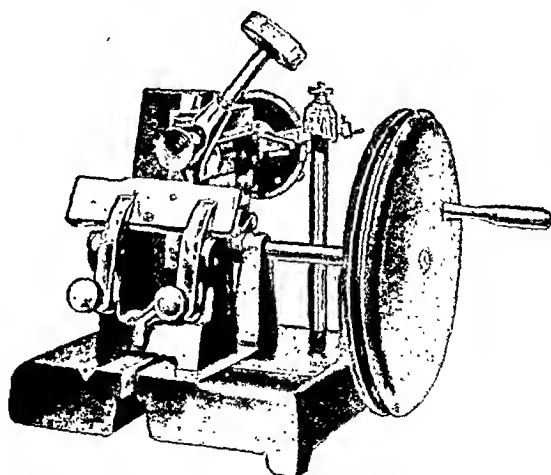
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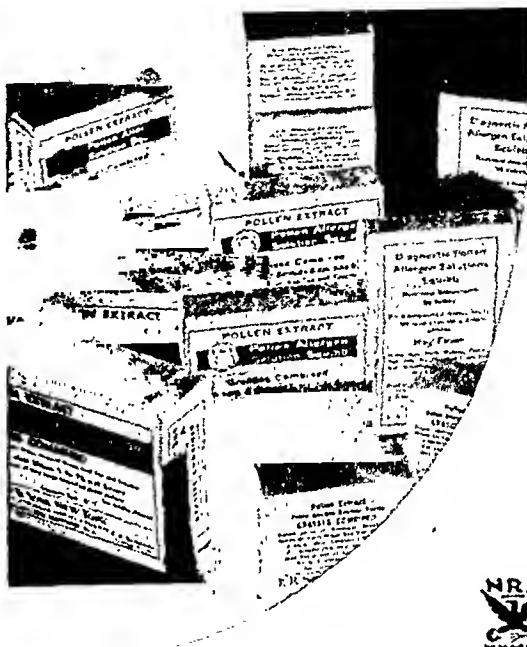
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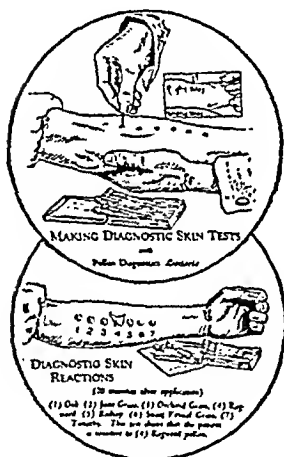
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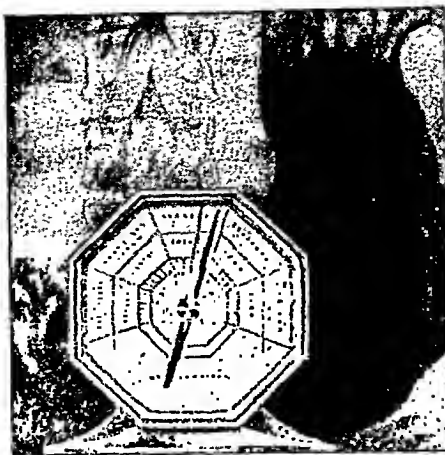
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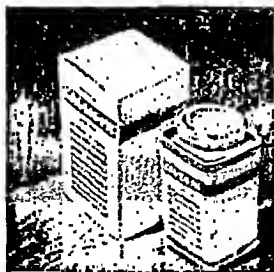
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"Dextri-maltose is a very excellent carbohydrate. It is made up of maltose, a disaccharide which in turn is broken up into two molecules of glucose—a sugar that is not as readily fermentable as levulose and galactose—and dextrin, a partially hydrolyzed starch. Because of the dextrin, there is less fermentation and we can therefore give larger amounts of this carbohydrate without fear of any tendency of fermentative diarrhea."—*A. Capper: Facts and fads in infant feeding, World J. Med., 1:278-282, 1928.*

In cases of diarrhea, "For the first day or so no sugar should be added to the milk. If the bowel movements improve carbohydrates may be added. This should be the one that is most easily assimilated, so dextri-maltose is the carbohydrate of choice."—*W. H. McCaslan: Summer diarrheas in infants and young children in Alabama, 1:278-282, 1928.*

"If there is an improvement in the teaching of the originator the carbohydrate added should be most easily assimilated. Dextri-maltose is therefore the carbohydrate of choice."—*Summer diarrheas in the young, International J. Med., 9:111-118, 1928.*

"The condition in which dextri-maltose is particularly indicated is in acute attacks of vomiting, diarrhea and fever. It seems that recovery is more rapid and recurrence less likely to take place if dextri-maltose is substituted for milk sugar or cane sugar when these have been used, and the subsequent gain in weight is more rapid."

"In brief, I think it safe to say that pediatricians are relying less implicitly on milk sugar, but are inclined to split the sugar element giving cane sugar a place of value, and dextri-maltose a decidedly prominent place, particularly in acute and difficult cases."—*W. L. Hoskins: Present tendencies in infant feeding, Indianapolis M. J., July, 1914.*

"Gradual transition to a whole milk or evaporated milk formula, which will supply about one and one-half to two ounces of whole milk to every pound of body weight, is reached. This also should finally have the addition of dextri-maltose amounting to five to seven per cent."—*R. A. Strong: Summer diarrheas in infancy and early childhood, Arch. Pediat., 19:221-222, 1902.*

## SERIOUSNESS OF DIARRHEA

There is a widespread opinion that, thanks to improved sanitation, infantile diarrhea is no longer of serious aspect. But Holt and McIntosh declare that diarrhea "is still a problem of the foremost importance, producing a number of deaths each year. . . ." Because dehydration is so often an insidious development even in mild cases, prompt and effective treatment is vital. Little states (Canad. Med. A. J. 13:803, 1923), "There are cases on record where death has taken place within 24 hours of the time of onset of the first symptoms."

In the treatment of diarrhea, "The sugar is added gradually as conditions admit, some sugar other than milk sugar or cane sugar being preferred, preferably dextrin and maltose."—*H. E. Small: Diarrhoea in bottle-fed infants, J. Maine M. A. 12:154-168, Jan. 1922.*

"It should be noted that a large percentage of sugar be required it is better to replace it by . . . 1's Nos. 1 and 2, where . . . in excess of the dextr . . . possibility of excessiv . . . earson: Common practices in infant feeding, Post-Graduate Med. J. 6:38, 1930; abst. Brit. J. Child. Dis. 28:162-163, April-June, 1931.

that group of organisms thrive on) and high in sugar (the food which is necessary to use the casein calcium for from 5-8 days; we then stopped it and added dextri-maltose to the formula."—*A. G. DeSanctis and L. V. Paider: The value of calcium caseinate milk in fermentative diarrhea, Arch. Pediat., 33:233-236, April, 1931.*

In diarrhea, "Carbohydrates, in the form of dextri-maltose, well cooked cereals or rice, usually can be handled without trouble."—*B. B. Jones: A discussion of some of the commoner infantile diarrheas, and the diets used in their treatment, J. Am. Med. Ass., 19:111-112, 1922.*

"Maltose is more easily absorbed than cane or milk sugar, and by changing the carbohydrate may prevent a deficient supply of sugar."

"When sugar causes diarrhoea, one can change the form of it. Mead's Dextrimaltose in small doses is more quickly absorbed and so superior to castor (leaves) sugar. Lactose is expensive and seems not to be better than castor sugar."—*H. B. Gladstone: Infant Feeding and Nutrition, William Heinemann, Ltd., London, 1928, pp. 11, 79.*

"The more complex carbohydrates, of which dextrin is the type, ferment more gradually and do not have this laxative effect."

Regarding the treatment of diarrhea, "In our experience, the most satisfactory carbohydrate for routine use is Mead's dextri-maltose No. 1."—*F. R. Taylor: "Summer Complaints," Southern Med. & Surg., pp. 555-559, Aug. 1928.*

"The sugar is added gradually as conditions admit, some sugar other than milk sugar or cane sugar being preferred, preferably dextrin and maltose."—*H. E. Small: Diarrhoea in bottle-fed infants, J. Maine M. A. 12:154-168, Jan. 1922.*

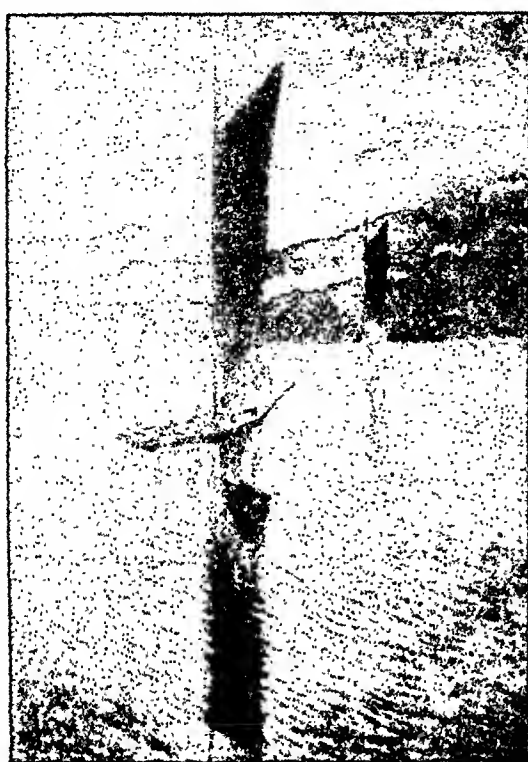
"It should be noted that a large percentage of sugar be required it is better to replace it by . . . 1's Nos. 1 and 2, where . . . in excess of the dextr . . . possibility of excessiv . . . earson: Common practices in infant feeding, Post-Graduate Med. J. 6:38, 1930; abst. Brit. J. Child. Dis. 28:162-163, April-June, 1931.

that group of organisms thrive on) and high in sugar (the food which is necessary to use the casein calcium for from 5-8 days; we then stopped it and added dextri-maltose to the formula."—*A. G. DeSanctis and L. V. Paider: The value of calcium caseinate milk in fermentative diarrhea, Arch. Pediat., 33:233-236, April, 1931.*

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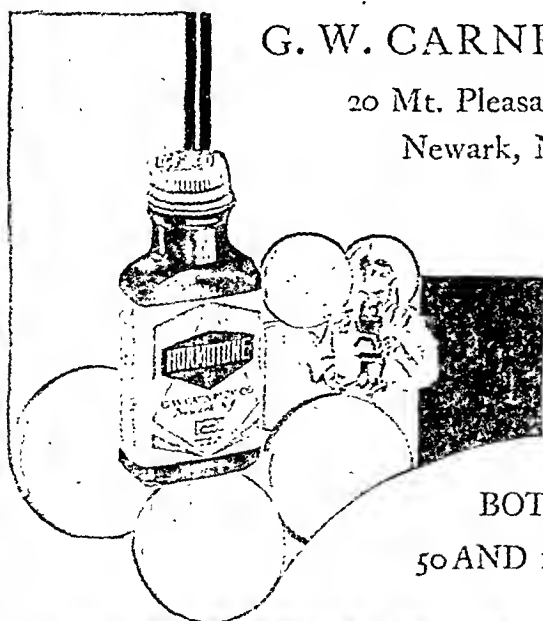
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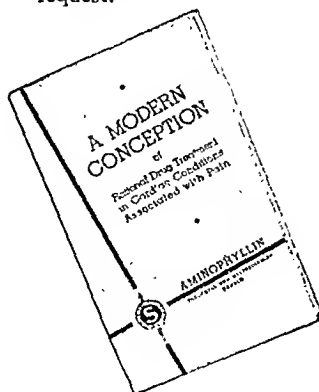
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MAY, 1934.

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ORIGINAL ARTICLES.

THE RELATIONSHIP OF POLYCYTHEMIA TO DUODENAL ULCER.\*

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To determine the relationship between two abnormal findings which are encountered in the same patient is sometimes a matter of great difficulty. There is the possibility of chance. If a causal relationship is suspected, it may be by no means easy to say which of the deviations from the normal is cause and which is effect. An illustration of the truth of these statements is afforded by the association of polycythemia and chronic duodenal ulcer, of which a certain number of cases have been reported within recent years.

Friedman, in 1913, described 6 cases in which a duodenal ulcer was demonstrated at operation, associated with definite polycythemia. In the only one of these which came to autopsy chronic pancreatitis was found. Friedman at that time stated that the literature did not contain a single reference to the association of erythrocytosis and duodenal ulcer. In 1914 he recorded an additional 11 cases. He believed that both the polycythemia and the duodenal ulcers were due to an outpouring of adrenalin into the blood stream. The fact that the leukocytes were not increased in number suggests that the polycythemia at least in some of these cases may have been an erythrocytosis rather than a true polycythemia vera. Bing,<sup>1</sup> writing in 1920, again refers to the relationship between polycythemia and duodenal ulcer as observed by Danish workers. In 1 of his own cases the red cells numbered 7,000,000 in

\* Read at the meeting of the Association of American Physicians, at Washington, D. C., May 10, 1933.

blood taken from the ear, and 8,200,000 in blood from the skin of the abdomen. He believes that gastric hypersecretion and repeated vomiting, by leading to concentration of the plasma, were the chief causes of the polycythemia, which would therefore be secondary rather than primary in character.

Polycythemia may be associated with gastric rather than duodenal ulcer. Weber and Watson<sup>11</sup> and also Schneider<sup>10</sup> have described such cases. In both of these cases there appears to have been a polycythemia vera with increase in the white cell count and hyperplasia of the bone marrow. In Schneider's case there was a marked degree of myocardial fibrosis (*vide infra*).

The case about to be described was characterized by polycythemia, leukocytosis, splenomegaly, duodenal ulcers, myocardial fibrosis, coronary artery occlusion, and marked ascites. The question whether the increased red cell count should be regarded as a true polycythemia or a secondary erythrocytosis is discussed below.

**Case Report.**—The patient, a man, aged 37, was admitted to the Winnipeg General Hospital under the care of Dr. Charles Hunter on October 12, 1932, complaining of enlargement of the abdomen and shortness of breath of a few weeks' duration, and of abdominal pain for the past 10 months. This pain, which was located in the epigastrium, was at first vague in character, but gradually became sharp and severe. It did not radiate, and was never accompanied by vomiting until a week before admission, when the patient vomited twice. It was relieved by taking food. The previous history was essentially negative. There was no complaint of dizziness nor other cerebral disturbance.

The chief feature of the clinical examination was the great abdominal distention, most of which was due to the presence of fluid, although the liver and spleen were found to be moderately enlarged. No cardiac abnormality was detected, apart from a soft apical systolic murmur. The electrocardiogram was normal. This is of particular interest in view of the subsequent postmortem findings. The systolic blood pressure was 140, the diastolic 96. A very slight degree of edema was present in both legs. Paracentesis resulted in the withdrawal of 3890 cc. of fluid, which was light yellow in color, with a specific gravity of 1.014, and an albumin content of 1 per cent. During the following 2 months paracentesis was performed on 9 occasions, the amounts withdrawn varying from 3280 cc. to 5400 cc. Urinalysis was negative. Gastric analysis showed normal free HCl and total acids. The stool occasionally showed traces of blood. The icterus index varied from 16.5 to 21, and the serum bilirubin from 2 to 2.9. The van den Bergh test gave a biphasic reaction. The urobilinogen varied from 1 in 10 to 1 in 60 dilution of urine. The bromsulphthalein test for liver function showed 10 per cent retention of the dye.

Repeated blood counts were made. The erythrocytes were always increased in number. The lowest count was 5,200,000, there were several just over 6,000,000, and the highest was 8,000,000. The hemoglobin varied from 90 to 118 per cent. On every occasion there was a well-marked leukocytosis, the lowest being 23,400, and the highest 34,350. The most striking feature of the differential count was the remarkably high percentage of polymorphonuclears, which varied from 89 to 97 per cent. No abnormal white cells were observed. The color of the face was high, particularly in the later stages, but this feature was not sufficiently striking to allow of a diagnosis of polycythemia vera.

During his stay in hospital the patient steadily lost weight. From 176 pounds on admission, his weight fell to 147 pounds shortly before his death which took place 2 months later. The shortness of breath mentioned on admission was not observed during the time that he remained in bed. At no time were the symptoms such as to suggest the possibility of a serious cardiac lesion. With the loss in weight, his general condition grew gradually worse. On December 10 he vomited several ounces of bloody fluid which clotted on standing. The vomiting continued, and he died on December 14.

*Postmortem Examination.* At the autopsy particular note was made of the high color of the face and upper part of the chest. The abdomen was hugely distended, but there was no edema of the legs. The abdominal distention was due to the presence of 2000 cc. of fluid, but there was no effusion in the pleural and pericardial cavities. The heart, which weighed 325 gm., was moderately dilated. Many large scars traversed the anterior wall of the left ventricle. At the apex of the heart the wall of the ventricle was extremely thin over an area 3.5 cm. in diameter. In this area there was an outward bulging of the cavity of the ventricle, if the expression may be allowed, but no bulging of the wall itself was visible on the outside. The inner surface of the herniation was of a dense white color, and presented yellow plaques and patches of calcification, so that the appearance closely resembled that of an atheromatous patch in the aorta. There was no sign of recent infarction. The valves were normal. At a point 1.5 cm. from the mouth of the left coronary artery, its anterior descending branch was occluded by a firm thrombus which filled the lumen as far as the vessel could be followed. Microscopic examination showed later that the occluding mass in the upper part of the vessel was of a very different character from that which filled the lower part. The part of the artery proximal to the thrombus was not atheromatous, nor was the right coronary. The aorta was also free from atheroma. The lungs merely showed edema.

The stomach and intestines were bright red in color and covered with a fine fibrinous exudate. The stomach was greatly distended, but showed no ulceration. On the anterior wall of the duodenum just beyond the pyloric ring there was a small ulcer 1.5 cm. in diameter. The ulcer was deep, its floor and edges were indurated, and in the base there was a small perforation which was responsible for the general peritonitis. Another chronic ulcer was present on the posterior wall, but this was much larger, measuring 2.8 cm. in diameter. The floor was formed by the head of the pancreas. The liver, weighing 2200 gm., was considerably enlarged. The outer surface was finely granular, and the cut surface showed a marked picture of chronic venous congestion. The portal vein was carefully examined for evidence of thrombosis or phlebitis, but none was found; the vessel was entirely empty of blood.

The spleen weighed 1000 gm. and was very greatly enlarged, but the greater part of its bulk was hidden by the ribs. The capsule was thickened. The organ was friable but quite firm. The cut surface was of a dark red color, and showed no infarcts. The splenic vein was examined for thrombophlebitis, but was found to be normal. The kidneys, adrenals, prostate and bladder were normal. The bone marrow in the long bones (femur, tibia, humerus) was abundant and bright red in color, giving every evidence of hyperplasia. The brain was not examined.

*Microscopic Examination.* Heart: Sections of the wall of the left ventricle show numerous areas of fibrosis with complete replacement of the myocardium. The apical lesion already described consists of extremely dense fibrous tissue.

*Left Coronary Artery.* In a section taken 6 cm. from the origin of the vessel the lumen is occupied by a mass of fibrous tissue which blends with a thickened intima. This mass presents 3 small channels which contain

red blood cells, and there are in addition a number of tiny lumina (Fig. 1). It is a typical picture of an organized thrombus which has become recanalized. The new channels are not only lined by endothelium, but each presents a separate internal elastic lamina. Sections of the proximal part of the artery show a uniform fibrous thickening of the intima without any evidence of atheromatous degeneration; in these sections the lumen is occupied by a fresh thrombus. The lungs are markedly congested; the alveoli contain many heart-failure cells. The liver is the seat of an extreme degree of central congestion, with complete disappearance of the liver cells in the affected areas; the peripheral zones are relatively intact. In the kidney the glomeruli are markedly congested and swollen, so as to occupy the entire capsular space. In the subcapsular zone, however, the glomeruli are shrunken, and many of the capsular spaces contain a large amount of plasma. In the pancreas there is practically no congestion; the acini show a patchy mucoid degeneration, and many of the islets, especially in the tail, are strikingly enlarged. In the spleen the lymph follicles are small and few and far between. The pulp is uniformly replaced by a diffuse arrangement of rather large cells, polyhedral or elongated, with vesicular nucleus and abundant cytoplasm. The endothelium lining the sinusoids is markedly swollen, and resembles in character the cells which replace the pulp. The amount of blood in the organ is not increased, nor is there any evidence of undue hemolysis. This is contrary to the opinion of Weber,<sup>11</sup> who considers that the splenomegaly is partially due to hyperplasia of the splenic pulp associated with increased hemolysis, but in agreement with the experience of Minot,<sup>8</sup> who found no postmortem evidence of hemolysis.

The duodenal ulcers present the usual picture of a chronic peptic ulcer (Fig. 2). The ulcerated surface is covered by necrotic material, and the submucosa and muscularis are replaced by dense fibrous tissue. The bone marrow of the long bones is in a condition of extreme hyperplasia. The fat of the yellow marrow is entirely replaced by large numbers of erythrocytes and normoblasts, and myelocytes are even more numerous (Fig. 3). It is a combined erythroblastic and leukoblastic hyperplasia.

*Comment.* The points which particularly call for discussion are: (1) is this a case of polycythemia vera or merely of secondary erythrocytosis? (2) what is the relation between the blood condition and the coronary thrombosis? (3) what is the relation between the blood condition and the duodenal ulcers? (4) what is the cause of the ascites?

1. The question of determining whether a case is one of polycythemia vera or of secondary erythrocytosis may be one of singular difficulty. Even so great an authority on the subject as Weber confesses his inability to decide the matter in many of the examples which he quotes. For one thing, it is not easy to state with exactness the exact level to which the red cell count must rise before it can be regarded as pathologic, and a count of 6,000,000 or even higher may be physiologic for certain individuals. In such persons, however, the leukocyte count is normal. Secondary erythrocytosis is frequently met with in conditions where there is an increased demand for oxygen, but in the case under consideration there is no indication that such a demand existed. Moreover, in secondary erythrocytosis the leukocytes are not increased in number, nor



FIG. 1.—Organized thrombus in coronary artery. Three new channels containing blood have been formed in the thrombus.  $\times 30$ .

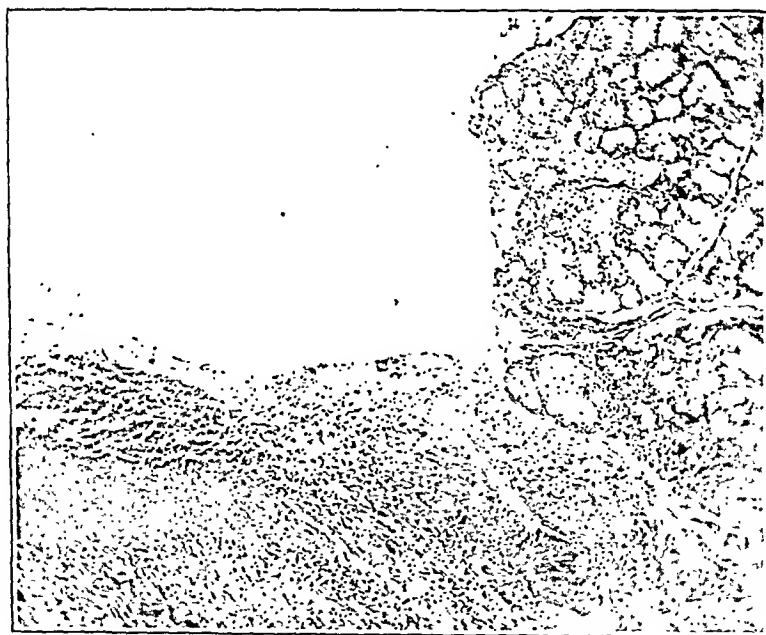


FIG. 2.—Duodenal ulcer.  $\times 40$ .



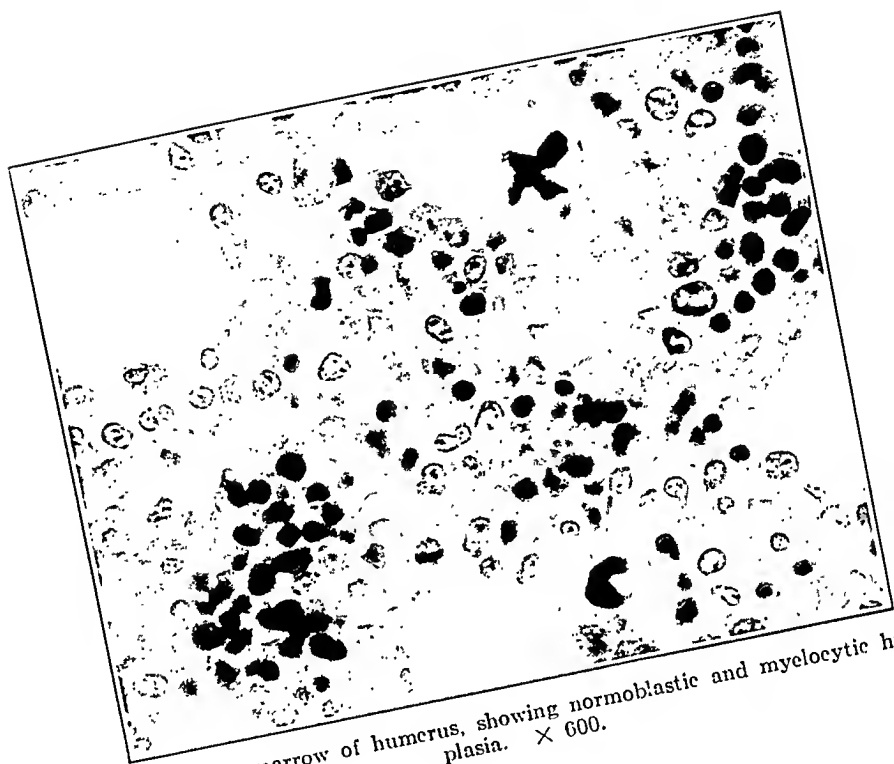


FIG. 3.—Bone marrow of humerus, showing normoblastic and myelocytic hyperplasia.  $\times 600$ .

does the bone marrow show the myelocytic response which was present in our patient. It may be suggested that the outpouring of fluid into the abdomen led to marked concentration of the blood with a resulting increase in the erythrocyte count, but this would not account for the hyperplastic marrow or the leukocytosis. For these reasons it appears justifiable to regard the case as one of polycythemia vera. Against this diagnosis is the absence of any marked cyanosis and of the cerebral and other symptoms which are characteristic of the condition. It is not unusual, however, as Christian and other writers have pointed out, for the patient to be pale. There may be a marked variation in the color of the skin, depending on such factors as the rate of blood flow and the state of the vessels.

2. It is not difficult to trace a relationship between polycythemia and coronary thrombosis. The literature contains many instances of thrombosis complicating polycythemia. In most of these the cerebral vessels have been involved, often with resulting softening of the brain; but thrombosis of the portal, mesenteric, splenic, renal and pulmonary vessels has been reported. The only record of coronary thrombosis which I have been able to find is Christian's 4th case, in whom there was bilateral thrombosis of the cerebral arteries and coronary artery thrombosis. In this patient the red cell count was 6,900,000, and the hemoglobin 180 per cent. The viscosity of the blood in polycythemia according to Harrop may be increased from 5 to 8 times owing to the great number of red cells, and this no doubt is the explanation of the tendency to thrombosis. In the present case it must be noted that the coronary artery presents evidence of two different thrombotic episodes. There must have been thrombosis of the distal part of the vessel on some former occasion, with organization and recanalization of the clot and production of the fibrotic lesion at the apex. The thrombus formation in the proximal part of the artery must have been a terminal occurrence.

3. The possible relationship between the polycythemia and the occurrence of duodenal ulcers is the most important question to be decided. The possibility that there may be no causal relationship must be admitted; the association may be purely accidental. On the other hand Friedman, Bing and others, as mentioned above, have described a number of cases in which both chronic duodenal ulcers and a markedly increased red cell count were present, so that the association in the present instance is in no way an isolated phenomenon. It is true that in these cases there is reason to believe that the increased cell count represented an erythrocytosis rather than a polycythemia vera, but in the cases of Schneider and of Weber and Watson there can be no question that the blood condition was a true polycythemia. As regards the question of a causal

connection between the two conditions it appears more probable that the tendency to thrombosis has manifested itself not only in the vessels of the heart, but also in those of the first part of the duodenum, producing in both a destructive lesion with necrosis of tissue. In Schneider's case of polycythemia vera there was an association of extensive myocardial fibrosis and gastric ulcer. Indefinite as is our knowledge of the etiology of peptic ulcer, it is generally agreed that the digestive juice acts upon some area of local necrosis or diminished vitality and that such a local lesion may have a vascular origin. For these reasons it is suggested that the relationship between the two phenomena is probably a direct causal one.

4. It must be admitted that the extraordinarily marked and rapidly recurring ascites refuses to fit into the general picture. Thrombosis of the portal vein would explain everything, as in the case of polycythemia described by Chauffard and Troisier, in whom ascites developed 5 months before death, and autopsy revealed chronic thrombophlebitis with complete obstruction of the splenic vein and the gastroepiploic veins. Manges also records a case of ascites associated with a red cell count of 8,000,000 and 35,000 leukocytes, but no autopsy was performed. In Monro and Teacher's case of splenomegalic polycythemia the lumen of the splenic vein was occluded by an old organized thrombus, which had become partially recanalized, in the same way that the coronary artery had been thrombosed and recanalized in the present case. Careful examination in our own case failed to reveal any thrombosis of the portal or mesenteric veins nor any evidence of phlebitis.

**Conclusion.** The association in a patient of polycythemia, coronary thrombosis and duodenal ulceration has been used as the basis of a discussion of the question as to whether the duodenal ulcers and polycythemia which may occur in the same patient, as described by several writers, are in any way related. The conclusion arrived at is that the polycythemia probably bears a causal relationship to the duodenal ulceration.

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## INTESTINAL INTUBATION: A PRACTICAL TECHNIQUE.

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THE desirability of intubation of the human small bowel beyond the duodenum for the study of intestinal physiology as well as for diagnostic and therapeutic purposes has been appreciated since the introduction of stomach and duodenal tubes. Isolated descriptions of its accomplishment have appeared from time to time, but none of the methods has proved practical, chiefly because of the time required for passage of the apparatus into the bowel and because the tubes employed have been too small to permit ready extraction of the jejunal or ileal contents. The apparatus which we have developed and the technique for its use which we will describe not only overcome these two objections, allowing ready passage throughout the jejunum, often into the ileum, and supplying an adequate lumen for the extraction of intestinal contents, but also permit simultaneous kymographic records of pressure changes within two areas of the upper half of the digestive tract or the injection of substances directly into the stomach, duodenum or the small bowel itself at any desired point above the termination of the tube. Furthermore, its introduction is little more disturbing to the subject than the passage of an ordinary duodenal tube, and it is easily and quickly removable by the mouth.

*Literature.* Scheltema,<sup>1</sup> in 1908, gave the first description of successful intestinal intubation, referring to it as permeation or sounding of the gastro-intestinal tract. In animals he was able to pass a small rubber tube through the entire tract, removing it per rectum, and finally accomplished intestinal intubation in a few children, using a tube of 3.8 mm. diameter (No. 11 F.) with a bulbous distal extremity. He referred to its possibilities for the introduction of medicinal substances in cases of intestinal parasites and cholera infantum, but apparently did not consider the aspiration of contents practicable. His tube was introduced by the nose and required several days to reach the small bowel.

In 1919, Einhorn,<sup>2</sup> unaware at the time of Scheltema's experiments, described the use of a soft rubber tube, 8 mm. in circumference (No. 8 F.), with an attached perforated capsule, for the injection of fluids into the intestinal tract. It, also, required much time

to reach the small bowel and was too small to permit aspiration of the contents. Buckstein,<sup>3</sup> in 1920, referred to the use of an intestinal tube for the injection of a barium mixture in order to study loops of the small bowel by the Roentgen ray. He was able to pass his tube 120 to 150 cm. beyond the teeth (60 to 90 cm. beyond the pylorus), and suggested its use for the study of the physiology and bacteriology of the small intestine. Einhorn,<sup>4</sup> during the following year, described a jointed tube of No. 8 F. size, made up of sections of 1 meter length, which he claimed permitted aspiration at 1 and sometimes 2 meter depths, but it was too small for extractions at lower levels. No studies on aspirated specimens were reported. In order to get this tube into the jejunum and ileum, repeated feedings and much time were required. A single case was referred to, the tube reaching the cecum on the 3d day; at that point it was employed for the instillation of medicated fluids as treatment for an ulcerative colitis; it was finally evacuated per rectum. Later, in 1923, he<sup>5</sup> reported its use in 2 other cases of ulcerative colitis: in these it required respectively 7 and 6 days for the tube to reach the cecum; in both the tube was removed by mouth.

Einhorn's jointed tube, while satisfactory for the instillation of fluids, has proved impracticable in our hands because of repeated failures to get it beyond the duodenum and upper jejunum, the time required and its small lumen. No further reports on its use have been discovered and it is not now manufactured.

*Apparatus.* The apparatus (Fig. 1) which we have finally developed has grown out of a considerable personal experience with various types used for experimental and clinical studies on the duodenum and small bowel. Its special virtues lie (1) in the fact that it has at its distal end a collapsible rubber bag, which, when distended, may be grasped by the peristaltic waves and carried along relatively rapidly in the intestine, and (2) in the fact that the tube has two lumina, one of which is used for inflation and deflation of the rubber bag while the other remains free for extraction and injection purposes.

Before securing a double-lumened rubber tube we experimented with two separate tubes, one within the other, this arrangement giving theoretically all the advantages of the present apparatus, but often the space between the walls of the two tubes, used for aspiration purposes, became occluded; also, the inner tube had too small a lumen to permit satisfactory kymographic records. It served, however, to demonstrate the practicability of our proposition for a double-lumened tube.

Much difficulty was encountered in having a double-lumened tube of sufficient length manufactured. About fifty of the more important producers of medical and special rubber goods in this country were visited or written to, but only one\* thought it possible to make such a tube and was willing to undertake some experiments.

\* U. S. Rubber Products Company of New York City.

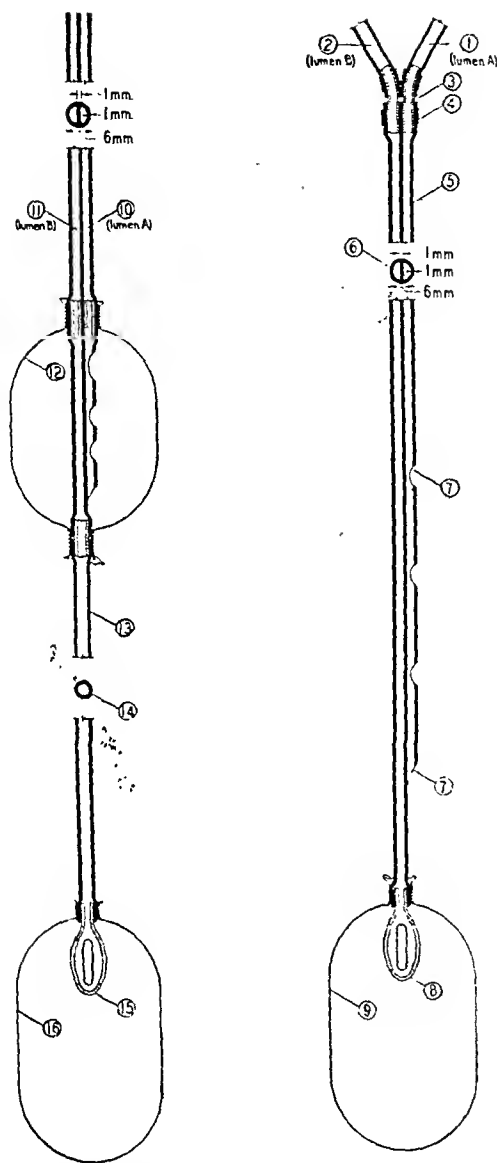


FIG. 1.—Longitudinal sections of double-lumened rubber tube (*right*) and of double-lumened tube with single-lumened tube attached (*left*). In each the lumen on the right side is referred to as "A" and the other lumen as "B." 1, indicates a proximal tube communicating with "A;" 2, one communicating with "B" (different colors); 3 indicates a brass cannula for making the connection between a lumen of double tube and proximal single tube; 4, thread holding two brass tubes in place; 5, outer wall of double-lumened tube; 6, transverse section of tube; 7, opening into lumen "A;" 8, Rehfuß bucket; 9, rubber bag (condom or finger cot); 10, lumen "A;" 11, lumen "B;" 12, rubber bag attached at proximal end over brass cannulae in two lumina, at distal end over single brass tube in lumen "B;" 13, single tube, connected proximally by means of brass cannula to lumen "B;" 14, cross section of single tube.

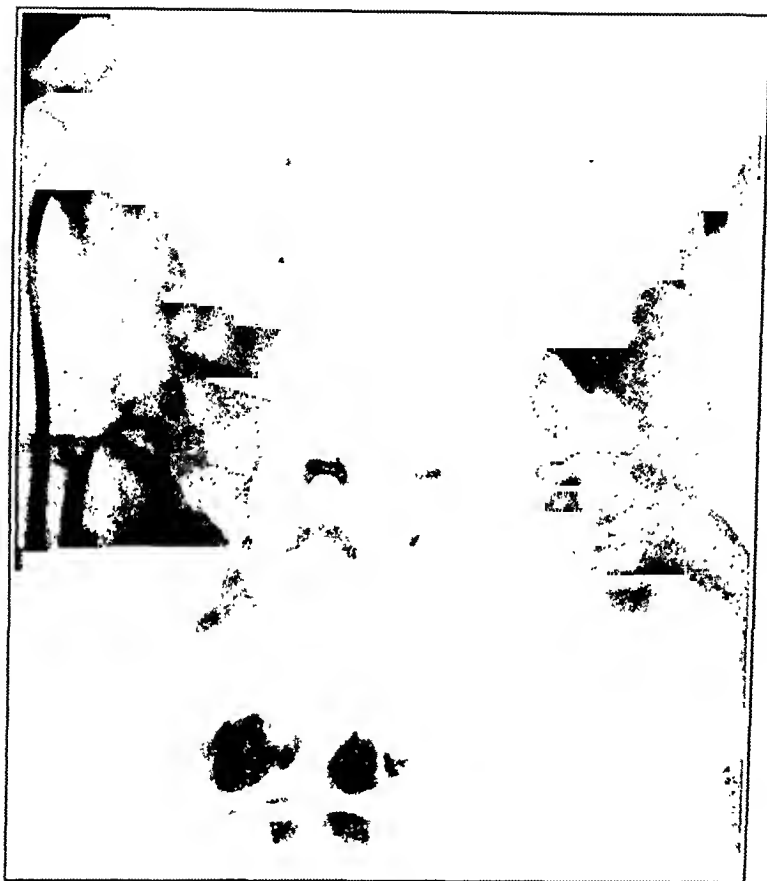


FIG. 2.—Roentgenogram showing apparatus in the stomach, duodenum, and upper half of the small intestine. The outer wall of one section of the double tube was cut away from the distal part of the tube, leaving only a single tube (lumen "B") beyond the arrow. Bag at distal end of lumen "B." This apparatus is useful for injecting substances into the bowel well above the distal end and for securing records of pressure changes from the bowel at the distal end of the tube. Lumen "B" and bag filled with 8% sodium iodid solution. (Postero-anterior view.)

That organization was finally able to supply us with the tube illustrated (Fig. 1). It has an outside diameter of 6 mm. (having, therefore, a caliber of No. 18 F.). Its walls and the partition are of 1-mm. thickness: the two lumina are of equal size, each a little larger than that of the ordinary duodenal tube. It is reasonably flexible, does not kink on sharp bending and has a fairly smooth external surface. An ideal tube would be slightly more flexible and have a smoother surface: we are trying to secure such a tube.

The details of the apparatus are given in the illustration and its legend. It is advantageous to have the two proximal rubber tubes (1 and 2 of Fig. 1) of different colors so that it is always obvious with which lumen each is connected. The duodenal or gastric metal capsule at the termination of the tube is not necessary but has seemed to render entrance into the duodenum easier; also, it serves as an end piece about which the bag may be attached.

It will be noted that one of the apparatuses illustrated consists of a double tube to which a single tube is attached. This is a convenient arrangement for obtaining two simultaneous kymographic records, or (when the proximal bag is omitted) for the injection of fluid substances at a distance above the termination of the apparatus. Other modifications will readily suggest themselves, and others have been employed by us.\*

*Technique.* The technique of intubation, as we have practised it, is simple. The tube with the bag deflated is taken by the fasting subject in the early morning, exactly as are gastric and duodenal tubes, only enough being swallowed at first to reach the stomach, and then with the subject reclining on his right side, more is introduced slowly until the distal end has reached the duodenum. Entrance into the duodenum may be determined by the character of the contents obtainable through lumen "B," or preferably by fluoroscopic observation. The special posture is no longer required but a little more tube is taken and fluoroscopic observations are made until the capsule has reached at least the third portion of the duodenum. Then the bag is distended moderately with air or an 8% sodium iodid solution (to render visualization of the tube and bag easier). After this the subject swallows about 5 cm. of tube every 10 min., fluoroscopic observations being made from time to time until the distal end has reached the desired point (Fig. 2).

We have found that within 6 hours the tube has usually passed along the bowel to a distance of 120 to 150 cm. beyond the pylorus. According to Einhorn the length of tubing required to reach from the pylorus to the cecum in the living human is approximately 270 cm.: this suggests that our tube usually reaches the half way point in the small bowel within 6 hours. In confirmation of this is the fact that fluoroscopic observation of a barium solution injected at the termination of a tube passed 120 to 150 cm. beyond the pylorus

\* This apparatus or special modifications of it may be secured through Edward P. Dolbey and Company, 3621 Woodland Ave., Philadelphia.



does not usually show evidence of valvulae conniventes, which are present only in the upper two-fifths of the small bowel, the jejunum; this indicating that the ileum has been reached.

Thus, without the necessity of having the subject take any food and within the early half of the day, the apparatus can be introduced into the upper ileum. Beyond this point it does not go so rapidly, probably because of the slight rigidity of the tube, but we anticipate that with an improved type of tubing even deeper penetration may be secured within the same period of time.

Once in the position desired the apparatus may be used for various purposes: with the bag inflated moderately and lumen "A" connected with a recording apparatus, continuous kymographic records of pressure changes may be secured; if the apparatus is equipped with two bags, simultaneous records from two areas may be obtained; when the bag is deflated, and the other lumen ("B") communicates with the interior of the bowel, aspirations may be made or substances may be injected at a fixed point.

*Value of the Technique.* It is not our purpose to refer to special studies made with this technique in this communication, but we may say that certain investigations of the chemistry and physiology of the small bowel are under way; also studies on the motor effects upon the bowel of drugs administered orally, by lumen "B" of the tube, and by hypodermic injection. Shiffer,<sup>6</sup> of our Section, using a modification of the apparatus, has perfected a technique for obturation of the lower duodenum and retrograde filling of that organ with an opaque substance which provides a satisfactory method for differentiating by the Roentgen ray certain obscure duodenal lesions. Bacteriologic study of the contents of the small bowel under fasting conditions and after the administration of certain types of food, also investigation of the anatomical relationships of the coils of the jejunum, are planned.

It is believed that this apparatus and the technique described furnish a direct means of studying many problems in the human that could not be attacked satisfactorily before, and it is hoped that other workers will become interested.

**Conclusions.** 1. A new apparatus, involving the use of a newly developed double-lumened rubber tube, for intubation of the human small intestine, and the technique for its employment are described.

2. By means of a rubber bag, attached at the distal extremity of the tube over an Einhorn or Rehfuß duodenal bulb and distended when it enters the lower part of the duodenum, the apparatus is pulled along the intestinal tract by peristaltic waves.

3. As now developed, the distal part of the apparatus will usually reach the upper ileum within about 6 hours, and it is believed that further developments may lead to even deeper penetration within the bowel.

4. The apparatus may be used to secure intestinal contents from,

or to inject substances into, any area within the upper half of the intestinal tract or to secure records of pressure changes from a fixed point of the tract or simultaneous records from two areas. It may lead eventually to new methods of diagnosing and treating intestinal lesions.

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## THE ENDOCRINE EFFECTS OF CERTAIN OVARIAN TUMORS.\*

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A PHASE of endocrinology which so far has remained almost untouched, at least in our American literature, is that dealing with the possible hormone effects of certain gonadal tumors, more particularly those of the ovary. This is rather surprising in view of the recognized hormonal influence of certain tumors involving other endocrine structures. To take the most conspicuous example, the adenomata of the pituitary, both those of the acidophilic and basophilic types, are accepted as bearing a causal relation to certain more or less clearly defined syndromes. Adenomata of the suprarenal cortex likewise have in some cases been shown to be responsible for the production of such syndromes as precocious puberty and virilism, and such syndromes have disappeared after removal of the tumors. With reference to the thyroid, such endocrine effects are not so clearly definable in the case of genuine neoplasms, whereas in the case of pineal tumors, a considerable number of reported cases would seem to indicate their capacity to evoke striking endocrine syndromes, involving practically always males, and characterized most often by such evidences of a disturbance of sex characters as premature maturity or hypertrichosis, often with obesity.

Such observations are explainable only on the basis of a persisting and excessive function of the tumor cells, so that even very tiny tumors are capable of evoking profound body changes. This is

\* Read before the American Association for the Study of Internal Secretions, Annual Meeting, Milwaukee, June 12, 1933.

strikingly illustrated in Cushing's description<sup>1</sup> of the amazing effects produced by even very small basophilic adenomata of the anterior pituitary lobe. Since the function of the constituent cells is apparently only an exaggeration of the normal function of the basophilic cells of the anterior lobe, it seems almost incredible that such massive total overfunction could emanate from such tiny lesions. Smith suggests as an explanation that under normal conditions the anterior hypophysis functions at a very low level, far below its full capacity, so that even a small mass of highly overfunctioning cells may bring about a violent endocrine upheaval.

As regards the ovary, it has long been known that certain tumors may produce remarkable changes in the individual, along both physical and physiologic lines. These changes are always in the nature of disturbed sex character differentiation, so that, in the consideration of this subject, we are at once thrown into the chaos surrounding the question of sex differentiation in general. Many different types of ovarian tumor have, if one may judge from the literature, been found in association with disturbances of the sex characters. It should be remembered, however, that most of these cases, especially those in the older literature, are incompletely or unauthoritatively reported, so that we are left in ignorance or doubt as to the pathologic diagnosis. Furthermore, in some cases coexistence of an ovarian tumor with a certain syndrome has led to the unwarranted assumption that the two are causally related, whereas a careful observation of the subsequent course would belie such an assumption.

A crucial test of the etiologic relation of ovarian tumors to endocrine syndromes is afforded by the disappearance or regression of the symptoms after removal of the tumors. This criterion has been applied most successfully in the case of certain ovarian tumors which had been generally unrecognized up to very recent years, and it is with these that this paper chiefly deals. Its object, briefly stated, is to show that certain ovarian tumors possess the capacity of hyperfeminizing the individual, so to speak, while others produce changes which must be interpreted as indicating a defeminization or masculinization of the female patient.

**Granulosa-cell Tumors of the Ovary.** These tumors are found most often in elderly patients, but may occur during the reproductive era, and occasionally in young children. They are made up of cells whose individual characteristics and arrangement, as well as physiologic function, are similar to those of the normal follicular epithelium. At times a tendency to the formation of actual follicles is noted, while in other instances the pattern is a much more diffuse one, and may be almost sarcomatous in appearance. I shall not here discuss the pathology and the histogenesis of these tumors, as this has been done fully in a paper to be presented before the Section on Pathology and Physiology of the American Medical Association

at the present session.<sup>2</sup> Suffice it to say that these tumors are now generally accepted as arising from granulosa-cell rests, representing follicular epithelium which has not been used up, so to speak, in the formation of the follicular apparatus of the ovary. This epithelium is a source of folliculin, so that it is not surprising that tumors consisting of this tissue have a distinctly feminizing tendency.

When these tumors occur in women well beyond the menopause, as is so often the case, they produce uterine bleeding which may or may not be free, but which characteristically is periodic, so that it presents clinically as an apparent reestablishment of the menstrual function. Uterine bleeding at this age is always to be looked upon with suspicion, as it most often indicates uterine cancer. Curettage in cases of granulosa-cell carcinoma yields an endometrium which is in no way suspicious of cancer, but which most often exhibits the hyperplasia pattern so characteristic of functional uterine bleeding in patients during the reproductive epoch, especially those approaching the menopause. There is no longer any doubt that this type of bleeding is an endocrinopathy, the immediate ovarian disturbance being a hyperfolliculinism. Corpora lutea are characteristically absent in such ovaries. There is considerable evidence that behind the ovarian disturbance is one involving the anterior pituitary sex hormones, but this question need not be discussed here.

The point to stress is that the clinical symptoms and the uterine changes associated with granulosa-cell tumors of the ovary, even in very old women, are exactly similar to those associated with excessive folliculin production in women of reproductive age. In each case the follicular epithelium plays the important rôle, so that it is easy to understand why these tumors are capable of bringing about such remarkable rejuvenation changes in the pelvic organs.

Even more striking, perhaps, are the effects produced by granulosa-cell tumors when they occur in children below the normal age of puberty. Only 3 such cases have been reported thus far, although to these I can add 3 more. These were reported in a paper read last month before the American Gynecological Society.<sup>3</sup> Children suffering from granulosa-cell tumors of the ovary characteristically develop the syndrome of precocious puberty, including precocious menstruation. The inauguration of the menstrual function is often preceded by a periodic vaginal discharge. Other manifestations are mammary overgrowth, precocious development of both the external genitalia and the uterus, the appearance of axillary, pubic and genital hair, and increased body growth, with a precocious development of the characteristic feminine contour.

Whatever the individual viewpoint may be as to the underlying cause of sex differentiation, and whatever one's views as to the relative importance in the human of the sex cells and the endocrines, there is no division of opinion as to the influence of the latter in the

production of the secondary sex characters, such as mammary development, growth of hair, etc. Here again the increased endocrine activity of the constituent tumor cells clearly explains the clinical syndrome which the tumor evokes. That overproduction of folliculin actually occurs in these cases has been further confirmed by studies of the folliculin content of the blood and urine in 1 or 2 cases, as well as by the effects produced by injecting tumor material into castrated animals.

I have been much interested in one aspect of this subject which, so far as I know, has received no attention in the literature. Certainly, it would seem that the only ovarian hormone concerned in this clinical picture is folliculin, and yet the associated uterine bleeding, in children or in old women, is often clinically indistinguishable from normal menstruation. This bears out the growing opinion that, insofar as the mere periodic bleeding of the menstrual cycle is concerned, folliculin plays the all-important rôle. Fluctuations in the folliculin level explain the whole bleeding process adequately, as investigators are more and more coming to believe, even though progesterin plays an essential rôle in other manifestations of human cyclical activity.

What factor, however, brings about the periodic drop in follicular level which is presumably the cause of the uterine bleeding? This question cannot yet be satisfactorily answered, but the importance of the withdrawal of either the ovum or corpus luteum influence, formerly rather generally assumed, is negated by the observations in cases of granulosa-cell tumors of the ovary. Here we have no ova or corpora lutea to deal with, and yet the bleeding may exhibit exactly the same periodicity as that of normal menstruation. We can only speculate as to the reason for this, but the one which suggests itself is that the folliculin factor is automatic and self-regulating, so that an excess of the hormone evokes some mechanism, possibly pituitary, bringing about a discharge of folliculin, with bleeding as a result. This explanation, as applied to normal menstruation, has already been suggested by various investigators, especially by Moore, although the evidence for its correctness is not yet complete.

**Arrhenoblastomata.** The other group of tumors to which I should like to refer produce effects upon the sex characters along quite opposite lines, in that they tend toward a defeminization and masculinization of the individual. For the recognition of this group, and for a rational explanation of their histogenesis and their pathologic physiology, we are indebted chiefly to the work of Robert Meyer,<sup>4</sup> who has suggested as an appropriate name for this type of masculinizing tumor the designation "arrhenoblastoma." Pathologically these tumors are to be classed as testicular adenomata, most often of the so-called atypical variety. It has long been known that certain tumors, not only of the ovary, but also of the

suprarenal, pituitary and pineal bodies, may be associated with loss of feminine characters and greater or less degrees of virilism. This is especially true of cortical lesions of the suprarenal, and a considerable group of cases of this sort have been reported in the literature. For the reader interested in this subject a good start may be obtained from the classic paper of Bulloch and Sequeira (1905)<sup>5</sup> and that of Glynn (1914).<sup>6</sup>

It is suggestive that many of the reports concerning ovarian tumors found with such syndromes speak of the tumors being of a "peculiar" or "puzzling" or "unusual" type. Various pathologic diagnoses have been made, such as carcinoma, sarcoma, endothelioma, hypernephroma, granulosa-cell carcinoma, etc. A review of these old cases suggests, in the light of our newer knowledge, that the tumors belong in the category of arrhenoblastomata.

A proper understanding of the histogenesis and biologic significance of these tumors, presupposes some familiarity with two still unclarified subjects, viz., the embryology of the ovary and the mechanism of sex differentiation in general. Neither of these can be discussed within the limits of a short paper. With reference to the development of the normal ovary, it would seem that there is a growing tendency against the older descriptions of von Winiwarter, Felix and others and in favor of the newer viewpoint, championed especially by Fischel,<sup>7</sup> that the real "Keimepithel" is not the germinal epithelium of the ovary, and that the latter is not responsible, as had been believed, for the formation of the follicular apparatus, through the formation of invaginating "medullary columns" and "Pflueger tubules."

According to the newer view, which is apparently substantiated by the large material on which Fischel's study is based, the follicular epithelium is formed by the cortical mesenchyme *in loco*, as a result of a direct transformation of some of the mesenchymal elements into epithelial cells. The latter then group themselves around the germ cells, which Fischel believes reach the sex anlage after migrating from the entoderm of the hind gut. The rete ovarii is likewise formed from the mesenchyme, and is the homologue of the rete testis of the male. Cells in this region may remain in an undifferentiated stage, so that it is understandable that tumors arising from them may develop along either male or female lines.

The close contiguity of the suprarenal anlage with that of the gonad, and the fact that both are derived, if the newer view is correct, from Wolffian mesenchyme, makes it easy to understand why cortical tumors of the suprarenal may give rise to a syndrome very similar to that produced by the tumors originating from the rete region of the ovary. This is particularly true if we accept the view, urged especially by Witsehi,<sup>8</sup> that the medulla of the gonad is a "determiner" of masculinity in the germ cell, just as the cortex is a "determiner" of femaleness. This view is supported by a wealth of biologic evidence.

What has been said represents in essence the concept of the origin of arrhenoblastomata which has been suggested by Meyer. It is at once obvious that this question cannot be separated from that of intersexuality, and that it will not be entirely clarified until we know more than we now do as to the factors concerned in the differentiation of the sexes. It may be emphasized, however, that these tumors do not characteristically arise in hermaphrodites or pseudohermaphrodites, but in individuals who had been quite normal before the development of the tumors. In this respect they differ from still another type of ovarian tumor which is becoming more generally recognized, the dysgerminoma or seminoma. The latter arise most often in very young individuals with defective gonads, and not infrequently in pseudohermaphrodites. The tumor itself has its origin in cells which have apparently lost all capacity for differentiation, so that no sex hormone influence, either male or female, is produced, and hence such tumors have no influence on sex characters. In other words, while they often occur in pseudohermaphrodites, they have no causal relation to bisexuality.

The arrhenoblastoma, on the other hand, often develops in previously normal individuals, and through its hormone influence, brings about a greater or less degree of sex reversal, with often a virtual pseudohermaphroditism. The tumor, arising from the undifferentiated cells of the rete region, develops in a male direction, and may thus overcome the feminizing influence of the ovarian follicular structures. This is a rather bald way of summing up a very abstruse subject, but that such tumors do actually produce this masculinizing effect admits of no doubt. Women with such tumors cease to menstruate, the breasts atrophy and flatten out, and a heavy growth of hair appears on the face, so that daily shaving may be necessary. The hairy growth may involve also the chest, abdomen and extremities. In a considerable number of cases the voice has become deeper and heavier, and the clitoris has not infrequently been markedly hypertrophied, so as to resemble the male organ. The configuration of the patient may lose the normal feminine curves and become lank and angular.

While these cases are rare, they are of exceeding interest from the standpoint of endocrinology, and perhaps even more from a general biologic viewpoint. They at once suggest a similarity with the instances of sex reversal observed in many of the lower animals. The free-martin of Lillie, the masculinization of hens after tuberculous destruction of the left gonad, the experimental reversal of sex in frogs and many other species—all these phenomena, and many others, come to mind in the consideration of the sex changes produced by arrhenoblastomata. Their discussion in this paper would lead us too far afield.

From a pathologic standpoint, these tumors are also of great interest. Their structure is quite variable. In the first place

tumors of well differentiated mature testicular tissue may occur in the ovary, the so-called testicular adenomata originally described by Pick.<sup>9</sup> These, however, most often have no effect on the patient's sex characters, while on the other hand the atypical testicular adenomata are highly potent from an endocrine standpoint. This may seem anomalous, unless we recall that pseudohermaphrodites with feminine external sex characters may possess well-developed testes, and only testes, with no ovarian tissue.

The tumors often present a rather sarcoma-like picture, but even then there is usually noted a tendency to the formation of small cords or strands of cells, while in other parts definite narrow and perhaps zig-zag tubules may be seen. The cells are oval, spindle or polyhedral in shape, and in a few cases larger cells, interpreted as interstitial cells, have been observed. For a fuller description of these tumors from the standpoint of pathology and histogenesis, I must again refer to the forthcoming paper by the present author, in collaboration with Long.

While both the arrhenoblastomata and the granulosa-cell carcinomata are classed as malignant, they are certainly relatively benign, and in the majority of cases, their removal has been followed by complete cure, with regression of the abnormal changes and the restoration of feminine characteristics, including the menstrual function. A striking demonstration of the causal relation of the tumor to the symptoms is found in the case of Kleinhans, described by Wagner,<sup>10</sup> in which regression of the symptoms followed removal of the unilateral tumor, with return of the masculinization later because of a recurrent tumor in the other ovary. In a small proportion of cases, the tumors, including those of the granulosa variety, have run a malignant course, with recurrence of the tumor after operation, and ultimate death of the patient.

As stated in the early part of this paper, somewhat similar influences have been attributed to other types of ovarian tumors than those which have been described. Ovarian carcinoma of one sort or another, sarcoma, cystadenoma, teratoma and other neoplasms have been held responsible for such manifestations of endocrine activity. There is no doubt that in many of these cases, especially those in the older literature, the tumors were really arrhenoblastomata or granulosa-cell tumors, or that one or other of the latter were associated with the larger tumors to which clinical importance was attached. With sarcoma it is easy to believe that there might actually in some cases be an endocrine function of the cells, if the growth has its origin in undifferentiated cells of the mesenchyma which, as we have seen, is probably the mother tissue of both the follicular epithelium and interfollicular connective tissue.

The only other tumor which, in rare cases, has shown evidences of endocrine activity is the so-called struma ovarii, in which, as a result of teratomatous growth, thyroid tissue is found in the ovary.



Moench,<sup>11</sup> Kovács,<sup>12</sup> and Masson and Mueller<sup>13</sup> have reported instances of this tumor in which the thyroid tissue in the ovary was obviously functionally active. In the case of Kovács, for example, the patient presented the clinical picture of Basedow's disease, and the symptoms disappeared after the removal of the ovarian tumor. Moench's case was somewhat similar, as were those of Masson and Mueller. I have personally observed no instance of this type.

**Summary.** Certain tumors of the ovary, like tumors of other endocrine glands, are capable of highly developed endocrine function. The two most clearly defined types are the granulosa-cell tumors and the so-called arrhenoblastomata, the latter belonging to the group of testicular adenomata, most often of atypical variety. The granulosa-cell tumors exert a feminizing effect, through the production of theelin by the tumor cells, so that in older women, perhaps far beyond the menopause, they produce most often a hyperplasia of the endometrium associated with periodic bleeding (pseudomenstruation), together with increased size of the uterus. In the few cases seen in very young children, they have produced the syndrome of precocious puberty, with precocious menstruation.

The arrhenoblastomata, on the other hand, have a definitely masculinizing tendency, as might be expected from the fact that they apparently have their origin from undifferentiated epithelium in the region of the rete ovarii. Under conditions which are not clear, these cells, capable of development along either male or female lines, may assume definitely masculine tendencies, as in the group of tumors under discussion. The relation of this endocrine cause of partial sex reversal to the general problems of intersexuality, sex differentiation and sex reversal is obvious, although our knowledge on these subjects is still far from complete.

Patients suffering from arrhenoblastoma present in the extreme instances not only such manifestations of defeminization as amenorrhea and breast atrophy, but also such evidences of masculinization as a masculine type of hair distribution, deepening of the voice, and hypertrophy of the clitoris. Removal of the tumor brings about a regression of these symptoms.

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# A STUDY OF ANHYDREMIA IN DIABETIC COMA.\*

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THE profound dehydration of the patient in diabetic coma results in two serious complications: anhydremia and anuria. Many observers have reported anuria as a frequent and fatal complication.<sup>1,2,3,4,5,6</sup> Peters and his coworkers<sup>7,8,9,10</sup> have studied the serum proteins in diabetic acidosis and conclude that their initial high level is due to blood concentration. Chang and Harrop<sup>11</sup> found the circulating blood volume reduced. One has only to refer to Marriott's<sup>12</sup> review of anhydremia to realize its effect, uncomplicated by ketosis, on the circulation and the ability of the kidney to excrete urine. He points out that after a period of dehydration the administration of water causes an immediate dilution of the blood and an abrupt fall in the concentration of hemoglobin. The blood concentration then gradually increases, the excess of water being in part excreted by the urine and in part taken up by the desiccated tissues. Ultimately if water continues to be administered a condition of equilibrium is attained between the tissues and blood, after which the concentration of the blood remains constant. In addition when anhydremia is present the secretion of urine is greatly decreased, the colloidal osmotic pressure, according to Starling,<sup>13</sup> approaching the arterial pressure in the renal arterioles. Albumin and casts are regularly present in the urine in conditions of anhydremia, suggesting an irritative disturbance of the kidney. In the patient in diabetic coma there are present not only the effects of anhydremia but the additional burden of ketosis. Not, however, until dehydration and anhydremia occur, does the complication of anuria occur. The patient going into diabetic coma excretes large amounts of urine, and as he almost always approaches

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the condition of coma slowly, there results from the excessive loss of water extreme dehydration and desiccation of the blood. The effect of this loss of water on the electrolyte balance has been reported in a recent study on 2 diabetic patients by Atchley and his coworkers.<sup>14</sup> Insulin was withdrawn and the patients allowed to develop a severe degree of ketosis. During this period there was a rapid loss of sodium and potassium. The continuance of such a loss would result in a depletion of base in the body enough to cause dehydration of the tissues and a decrease in blood volume.

We are reporting 8 cases of diabetic coma in which a study was made of the blood concentration and the effect of treatment on this concentration.

**Procedure.** The patients were admitted to the wards of the Third (New York University) Medical Division of Bellevue Hospital. On admission each patient was given an enema of 1000 cc. of physiological saline solution and the return fluid was measured. A gastric lavage of 1000 cc. of saline was also given and the return measured. A sample of blood was taken immediately under oil, and without a tourniquet to avoid stasis. The patient was then catheterized and treatment was begun. This consisted of infusions of saline, to each 1000 cc. of which 50 gm. of glucose was added, and insulin intramuscularly every half hour. The initial dose was usually 40 units and the subsequent doses varied from 25 to 20 units.

The blood was analyzed as follows: the  $\text{CO}_2$ -combining power of the plasma was done according to the method of van Slyke and Cullen;<sup>15</sup> blood sugars by the Folin-Wu method;<sup>16</sup> non-protein nitrogen by the Folin-Wu method;<sup>17</sup> hemoglobin determinations were done by the Newcomer method<sup>18</sup> and were read in a Klett colorimeter. The hematocrit<sup>19</sup> readings were made in sedimentation tubes. The readings give the volume of cells in per cent. The total solid content of the blood was done on whole blood and in some of the cases on plasma as well. The procedure for this was as follows: the blood having been drawn under oil was placed in bottles containing a weighed and constant amount of oxalate. One cubic centimeter of blood was drawn up into standardized 1-cc. volumetric Ostwald-van Slyke pipettes and run into a weighing dish. This was immediately weighed and the blood then dried in an oven at  $80^\circ \text{C}$ . until a constant weight was reached. The dried weight was divided by the weight of the volume of blood used and the solid content of the blood reported in per cent. All total solid determinations, hematocrit readings and  $\text{CO}_2$ -determinations were done in duplicate.

**Results.** Table 1 summarizes the results obtained. Four of the 8 cases died. Autopsies were performed on 3 of these. In Case 6, aged 51, postmortem examination showed in the lungs hypostatic congestion and edema. There was a chronic adhesive pleuritis of the right lower lobe and an interlobar plastic pleuritis. The heart showed myocardial fibrosis, arteriosclerosis of the mitral and aortic

valves and a mild degree of coronary sclerosis. There was slight dilatation of the ascending aorta and mild atherosclerosis. The liver weighed 1520 gm. It was hyperemic, microscopically there was cloudy swelling and evidences of chronic passive congestion. The spleen was hyperemic. There was chronic passive congestion of the pancreas and sclerosis of the vessels. The interstitial fibrous tissue was increased and the islands of Langerhans were atrophic. The kidneys showed nephrosclerosis of the arterial and arteriolar type. In Case 8, aged 59, postmortem examination showed a lobular pneumonia of the left lung and pleural edema of the right side. There was bilateral adhesive pleuritis and generalized congestion and edema. In the heart the ventricular endocardium was fibrotic and there was chronic valvulitis of the mitral valve. The liver weighed 2675 gm. There was enlargement with marked fatty changes. Microscopically there was practically no normal liver tissue, the section seemed to consist of fat with atrophic degenerated liver cords. The pancreas showed interstitial fibrosis and fat replacement. The kidneys were normal. In Case 11, aged 55, postmortem examination showed congestion and edema of the lungs. There was arteriosclerosis of the mitral and aortic valves and sclerosis of the coronary vessels. There was diffuse atherosclerosis of the aorta with a moderate degree of calcification. The spleen was soft and there was follicular hyperplasia. The liver and the diaphragm.

TABLE 1.—SUMMARY OF TREATMENT WITH FLUID INTAKE AND URINE OUTPUT DURING THE PERIOD OF KETOSIS.

Case No.	4.	6.	7.	8.	9.	10.	11.	12.
Name . . . . .	A. B.	H. S.	J. B.	M. O'S.	E. O'C.	M. B.	M. B.	J. K.
Age . . . . .	16	51	42	59	65	16	55	22
Duration of diabetes . . . . .	10 yrs.	8 yrs.	Unk.	Unk.	3 mos.	9 mos.	1 yr.	9 yrs.
Duration of present symptoms . . . . .	12 hrs.	24 hrs.	?	3 days	2 hrs.	2 wks.	2 wks.	18 hrs.
Complications . . . . .	None	None	Vincent's angina	None	Chr. Tbc.	None	None	None
Hours before acetone free . . . . .	10½	12½	7	13	13	11½	15½	10
Insulin units . . . . .	360	390	190	290	220	215	180	350
Carbohydrate (grams) . . . . .	285	300	150	325	385	310	210	338
Fluid intake (cc.) in period when pt. became acetone free . . . . .	7030	8400	4975	8500	5040	9270	9025	8850
(a) Per cent as infusion . . . . .	29.1	35.7	21.1	47.1	29.7	32.4	11.0	20.3
(b) Per cent as elysis . . . . .	28.5	47.8	30.2	23.5	0	21.6	22.2	22.6
(c) Per cent by mouth and rectum . . . . .	32.4	16.5	48.7	29.4	70.3	46.0	66.8	57.1
Urine output (cc.) . . . . .	1640	759	888	1277	3140	6100	2068	2590
Outcome . . . . .	Good	Death	Good	Death	Death	Good	Death	Good
Ratio of urine output to fluid intake . . . . .	1:4.2	1:11	1:5.6	1:6.9	1:1.5	1:4.3	1:4.3	1:3.4

There was fatty degeneration and microscopically there was practically no normal parenchyma seen. In the pancreas there were very few islands of Langerhans remaining and those present were hyalinized. Throughout the parenchyma there were numerous strands of fibrous tissue. The kidneys showed a bilateral pyclo-nephritis with abscess formation in the right kidney. All of the patients who died were over 50 years of age and 3 had been ill for

24 hours or more before admission to the hospital. The previous duration of the symptoms of coma have a very important effect on the outcome of the case. The patient whose symptoms were of shorter duration was complicated by a chronic tuberculosis. All of the patients who died were acetone free at the time of death.

Table 4 summarizes the blood findings before and after treatment in the 8 cases. Tables 2 and 3 show the results in detail on Cases 10 and 11, 1 of which (Case 11) died. In 5 cases the total solid content of the blood indicated blood concentration. Of the 3 cases in which the total solids were not high, Case 9 was definitely anemic. In Case 6 enough blood could not be obtained for analysis until the patient had received fluids intravenously so that the first reading reported is after treatment. In Case 7 the patient was not actually in coma, although there was no doubt that he was rapidly approaching that state.

TABLE 2.—DATA IN CASE 11, M. BR., 55 YEARS, FEMALE; CONDITION ON ADMISSION: COMATOSE.

	Findings on admission.	Period elapsed from time of admission.			
		1½ hrs.	5½ hrs.	10 hrs.	15½ hrs.
<i>Blood:</i>					
Total solids, per cent	28.75	26.3	20.75	20.7	20.45
Hemoglobin, per cent	.....	78.8	80.0	88.2	75.2
Hematocrit cell vol. per cent	38.0	36.5	41.5	41.0	36.0
Blood sugar mg.	512.0	512.0	444.0	425.0	235.0
Blood NPN mg.	75.0	46.0	41.0	43.0	35.0
CO <sub>2</sub> vol. per cent	5.0	8.0	27.0	31.0	33.0
Blood pressure	120/70	110/65	.....	156/55	120/65
<i>Urine:</i>					
Vol. (cc.)	240	255	900	233	680
Sugar (gm.)	4.0	12.0	Pres.	7	22
Acetone	4+	4+	3+ to 1+	1+ to 4+	1+
Diacetic	4+	4+	0	1+	0
Albumin	2+	2+	0	1000	3230
Fluid intake (total)		2000	2795		
Amount given by:					
Infusion		1000	.....	1000	2000
Clysis		.....	2795	.....	1230
Mouth		1000	100	40	35
Insulin units		80	120	30	40
Carbohydrate (gm.)		90			

Fluid intake until acetone free, 9025 cc.  
 Urine output until acetone free, 2068 cc.  
 Time until acetone free, 15½ hours.

He was dehydrated but, although the fluid content of the blood was decreased, anhydremia was not marked. In other cases a drop in total solids occurred which ranged from 8.3 per cent to 2.4 per cent. This corroborates the findings of Peters<sup>9</sup> and Atchley<sup>14</sup> that dehydration causes a severe anhydremia in patients in diabetic

coma. One realizes also that blood sugar or nitrogen determinations in such concentrated bloods are not true estimates. Since they are reported in milligrams per cent, a reduction of the fluid content increases the relative concentration. In Case 11 the non-protein nitrogen of the blood fell 40 mg. during the period when the total solid fell 8.3 per cent. Peters<sup>9</sup> also found that the non-protein nitrogen fell as diuresis was established. In Cases 6 and 8 in our series, the high non-protein nitrogen persisted in spite of blood dilution and in neither of these cases could diuresis be established.

TABLE 3.—DATA IN CASE 10, M. B., 17 YEARS, MALE; CONDITION ON ADMISSION: COMATOSE.

	Findings on admis- sion.	Period elapsed from time of admission.				
		3 hrs.	6 hrs.	11 hrs.	17 hrs.	Next day.
<i>Blood:</i>						
Total solids, per cent	24.4	20.9	21.55	22.3	24.5	21.4
Hemoglobin, per cent	111.0	89.4	99.0	....	97.0	94.0
Hematocrit cell vol. per cent	50.0	40.0	42.0	39.0	40.0	37.0
Blood sugar mg.	246.0	444.0	435.0	345.0	333.0	345.0
Blood NPN mg.	....	44.0	20.0	20.0	20.0	20.0
CO <sub>2</sub> vol. per cent	13.0	17.0	19.0	....	30.0	58.0
Blood pressure	150/90	150/85	135/80	144/102	122/80	118/66
<i>Urine:</i>						
Vol. (cc.)	210	1530	2790	1780	1585	2020
Sugar (gm.)	2.0	21.7	69.5	50.2	34.7	38.0
Acetone	4+	4+	2+	1+	Tr.	0
Diabetic	4+	2+	0	0	0	0
Albumin	4+	4+	3+	3+	3+	0
Fluid intake (total)	....	2500	4250	2520	1230	
Amount given by:						
Infusion	....	2000	1000			
Clysis	....	....	2000			
Mouth	....	500	1250	2520	1230	
Insulin units	....	120	40	55	20	
Carbohydrate (gm.)	....	130	110	70	70	

Total fluid intake until acetone free, 9270 cc.

Total urine output until acetone free, 6100 cc.

Time until acetone free, 11½ hours.

In 3 of the 4 fatal cases the diastolic blood pressure was persistently low and in all 4 the systolic pressure was low for the age of the patients, never reaching more than 120 mm. This is an important factor in increasing the tendency to anuria. If the blood pressure cannot be raised to a normal level for the individual and kept at this level, the prognosis is poor, and even if the blood is diluted the urine output remains low. Several observers<sup>5,6,9</sup> have found transfusion useful in raising the blood pressure in such cases. The course of the blood pressure is an indication of the progress of the case.

The relation between urine volume and blood dilution is shown in the individual charts of the patients. In the 4 cases that recovered an increased urine output accompanied the diluting of the blood fol-

lowing the intravenous administration of saline. When the dilution was not accompanied by any rise in blood pressure, as in Cases 6 and 8, the urine output remained low and continued administration of fluids was ineffective in increasing it. The total solid concentration of the blood did not always remain low after its initial drop. In Cases 4, 8 and 10 there was a rise above the initial concentration, but in all cases it dropped again. This rise in total solids was not accompanied by an increase in the percent of hemoglobin but was reflected to a moderate degree in the hematocrit readings. In Case 4 the increased blood concentration was directly proportional to a drop in fluid intake. During the first  $1\frac{3}{4}$  hours the patient received 1410 cc. of fluid, 1000 cc. in an infusion. Following this the total solids fell 0.55 per cent. In the next  $1\frac{3}{4}$  hours the patient received no infusion and only 210 cc. of fluid by mouth and the total solids rose 1.6 per cent. Again an infusion was given and the total solids fell 1.1 per cent. The urine output reflected the blood concentration. In Case 8 the blood concentration rose in spite of continued administration of fluids, only to drop again to a level lower than on admission in the next 3 hours. In Case 10 after an initial drop of 3.5 per cent the total solids rose slowly and after 17 hours were the same as on admission. This again was apparently a reflection of the amount of fluid administered and also perhaps of the route used. When infusions were given the fall was abrupt and remained lower. When the fluids were given by mouth and the amount was reduced, a gradual rise occurred. The urine output in this case was always good. Cases 9 and 11 both had a good urine volume following blood dilution, and in both there was a temporary rise in blood pressure. Peters<sup>9</sup> noted a tendency for the serum to remain concentrated throughout the first periods of treatment, in spite of administering large amounts of fluid, and to become diluted later even when small amounts were given. Case 9 died suddenly, apparently of circulatory collapse. Whether the low blood sugar of 54 mg. was a factor in bringing this about, it is impossible to say.

In all 8 cases there is a marked difference between the fluid intake and the urine output. The latter only represents a part of the fluid output of the body and we did not attempt to estimate the water put out through the lungs or the skin. The differences, however, are so great that one can gain a fair idea of the degree of dehydration by the amount of fluid retained. In Case 7, where it was possible to weigh the patient, in  $17\frac{1}{2}$  hours there was a gain of  $7\frac{1}{4}$  pounds. In Table 1 we have shown the ratio of fluid intake to urine output during the period of time that the urine became acetone-free. In Cases 9 and 10 the differences are not as marked as in the other cases, in which at least three times as much fluid was given as was put out in the urine. In Cases 6 and 8, both of whom died, the difference was marked. These were the cases with persistently low blood pressures.

TABLE 4.—BLOOD FINDINGS ON ADMISSION AND AFTER TREATMENT.

No. Case	Age.	Total solids %		Hemoglobin %		Hematocrit.		Blood sugar mg.		NPN mg.		CO <sub>2</sub> vol. %		Blood pressure.		Result.
		On admission.	After treatment.	On admission.	After treatment.	On admission.	After treatment.	On admission.	After treatment.	On admission.	After treatment.	On admission.	After treatment.	On admission.	After treatment.	
4	17	22.25	19.85	94.7	72.3	46.5	37	500	99	42	30	17	50	128/75	118/84	Improved.
6*	51	21.65*	19.35	84.0	74.6	75.0	37.0	476	500	67	57	8	..	70/48	76/58	Died.
7	42	21.35	20.1	....	87	42	36	212	200	36	36	41	51	110/80	110/75	Improved.
8	59	23.4	20.9	121	94	54	46	454	417	86	75	20	24	98/64	120/64	Died.
9	65	17.3	17.4	73.5	69.4	34	34	270	54	22	17	32	55	122/58	110/50	Died.
10	17	24.4	21.4	111	94	50	37	246	345	..	20	13	58	150/90	118/66	Improved.
11	55	28.75	20.45	....	75.2	38	36	512	235	75	35	5	33	120/70	120/65	Died.
12	22	25.0	22.0	....	94.7	42	47.5	444	113	32	20	13	33	144/90	112/80	Recovered.

\* Taken after 3000 cc. of fluid had been given.



**Discussion.** There seems to be little doubt that blood concentration is present in patients in diabetic coma. In discussing the nature of diabetic acidosis, Peters<sup>10</sup> stresses the importance of blood concentration, shock and the low blood pressure in producing the symptoms. Alkali deficits of the degree found in diabetic acidosis may be produced experimentally or may occur in other diseases without causing the clinical state encountered in diabetic coma. We have already pointed out that until dehydration and anhydrema supervene, the patient is not comatose. That this state of dehydration is the result of the extreme diuresis which accompanies the glycosuria resulting from the uncontrolled diabetic state is shown in the 2 patients studied by Atchley and his coworkers.<sup>14</sup> During the period of insulin withdrawal the water content of the blood fell gradually so that at the end of the ketosis period it had dropped 1.4 per cent in 1 case and 0.5 per cent in the second. During this time in each case the positive water balance became negative. The total solid concentration in 5 of our cases shows how far this loss of fluid from the blood can progress.

Observations such as these accent the importance of treating the diabetic patient in coma, not only for the existing ketosis, but also for the profound dehydration and the loss of fixed base that has occurred as a result of the diuresis. Insulin will correct the disturbed carbohydrate metabolism. It will render available that base from which bicarbonate has been displaced by ketones within the body,<sup>10</sup> but it cannot replace the available base that has already been excreted in the urine.

We have found no difficulty in giving large amounts of saline infusions, provided the blood pressure can be maintained. The patient in Case 10 in the present series is an uncoöperative patient, who stops taking his insulin at intervals. He has been admitted four times in coma since the admission reported here. On each occasion he has received from 4000 to 6000 cc. of saline by vein. When infusions fail to raise the blood pressure, transfusions should be tried.

**Summary.** Eight cases of diabetic coma are reported. Of these, 5 showed extreme desiccation of the blood as measured by the total solid concentration.

Following infusions and fluid the total solid concentration fell.

Of the 8 cases, 4 died. In these 4 the blood pressure, especially the diastolic, remained persistently low. All of the patients who died apparently had circulatory collapse. Autopsies were done in 3 cases. One had myocardial fibrosis and coronary sclerosis, 1 fibrosis of the ventricular endocardium and the third, sclerosis of the coronary arteries, any of which may have contributed to the circulatory failure.

The fluid intake during the period of ketosis exceeded the urine output.

The importance of fluids in treatment of diabetic coma is stressed.

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AUTOGENOUS VACCINES IN RHEUMATOID ARTHRITIS. A  
CLINICAL STUDY AND CRITIQUE.\*

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FREIBERG,<sup>1</sup> Klinge<sup>2,3</sup> and others<sup>4,5</sup> have demonstrated that arthritic changes ensue if an antigen is injected into a previously sensitized animal's knee joint. They have interpreted these changes as evidence of an allergic arthritis. Later Freiberg and Dorst<sup>6</sup> presented data which they considered proof that certain cases of rheumatoid arthritis were allergic in nature. They described the method employed in isolating and identifying the organism which

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represented the offending antigen as well as the manner of preparation and administration of the desensitizing vaccine. Their method is therefore briefly summarized. It consists in making cultures from postnasal secretions, infected sinuses, teeth, tonsils and feces. All the organisms obtained on various types of media and under differing gas tensions are isolated in pure culture, heat killed and intradermal skin tests made with each strain. Individual sensitivity to an organism is shown by marked redness, induration and local heat appearing 24 to 36 hours after injection. In other words, the presence of a positive skin test postulates that the offending organism, to which the patient is sensitive, has been isolated. Therapeutic success now depends only on desensitization with minute doses of such organisms. The importance of such work, if established, is obvious, because it not only adds considerably to our understanding of the etiology of rheumatoid arthritis but also puts vaccine therapy in the treatment of this disease on a simple, workable basis.

The study which we wish to present in this paper has been carried out in an attempt to evaluate critically the soundness of this method of determining a patient's susceptibility to autogenous organisms. We realize the difficulty in the interpretation of this method obtained over a comparatively short period of time in conditions like chronic arthritis. We have therefore restricted ourselves to making intradermal tests with organisms isolated from foci of infection as well as from the upper respiratory tract and feces in a series of patients with rheumatoid (atrophic) arthritis. However, in order to avoid misleading and fallacious interpretation of the results obtained, we controlled each intradermal test by making similar tests with each strain on three other subjects.

Before reporting our results, we should like to discuss briefly the value of some of the methods used in determining the specificity of vaccines in rheumatoid arthritis. The methods employed are based on the assumption that rheumatoid arthritis is a disease caused by various bacteria of low-grade virulence. This assumption is entirely hypothetical and the best evidence which supports it, the cultivation of streptococci from the blood and synovial fluid of arthritic patients by certain authors,<sup>7,8</sup> is contradicted overwhelmingly by negative results of others.<sup>9,10,11</sup>

To prepare vaccines which are believed to be specific, with the implication that the strains thus isolated from foci of infection and from the throat, stools, etc., are responsible for the disease, the following methods are used: (1) Complement fixation with the patient's serum;<sup>12,13</sup> (2) the growth-preventing effect of the patient's blood on the strains;<sup>14</sup> (3) the specific sensitiveness of the patient's skin to the vaccines prepared from the different strains.<sup>6</sup>

If these methods gave clear cut and consistent results, they would furnish valuable information concerning the etiological agent. The results previously published are far from doing so and offer

no evidence for the usefulness of these methods in the preparation of vaccines. In order to place dependence upon any one of the above-mentioned methods, one must have the assurance that they are reliable when applied to diseases caused by known bacteriologic agents. Observations of this sort have never been reported. The application, therefore, of such methods to diseases of unknown etiology is not valid. It is highly probable that random examination of a large number of different strains, isolated from various sites in the body by the recommended methods, would not permit us to find with any regularity the correct organism in such diseases as diphtheria, tuberculosis, the typhoid group of infections, chronic gonorrheal infections, etc. In diphtheria, for example, even if we should hit on the right strain, a heated suspension of the bacteria would probably give no complement fixation, and, since the diphtheria toxin is destroyed by heat, no specific skin test. In typhoid fever and paratyphoid infections, the specific bacteria are present only in small numbers in the majority of stools. Therefore, even if one examined 10 to 20 strains selected at random, he could expect to identify very rarely the causative organism either with the complement-fixation reaction or with skin tests. Without special methods, it is impossible to cultivate from a sputum tubercle bacilli which, after cultivation, would give specific skin tests. In chronic infectious diseases the difficulties are greater than in acute processes. If we suppose that rheumatoid arthritis is induced by a certain bowel or throat strain, there is no reason to expect to find the same strain several years afterward in the same location or in infectious foci of later origin.

When we come to examine the application of the different methods in practice, we must say that they are usually applied without the necessary controls and give no information as to the significance of the bacterial strain isolated. Shuster<sup>13</sup> often obtains varying results in the complement fixation with the same strain and believes at least 3 consecutive positive examinations are necessary to determine their specificity. Knowing the difficulties which have been encountered in tuberculosis and gonorrhea with the complement-fixation test, and that no generally accepted opinion exists concerning its value, we believe that no significance should be attributed to a varying test when applied to a strain of unknown etiologic significance.

The theoretical foundations of the growth-preventing effect of the blood for the selection of bacterial strains seem equally insecure. There are no observations published which show that the specific bacterial agent in chronic infections grows better in the patient's blood than in other human blood samples. On the contrary, in the majority of chronic infections a marked resistance develops against the invading bacterium and we should expect an increase rather than a decrease of the bactericidal effect of the blood.

TABLE 1.—RESULTS OF SKIN TESTS WITH VACCINES IN ARTHRITICS AND CONTROLS.

Case number.	Vaccine number.	Strain.	Source.	Diameter of reaction in mm. at 24 hours in:			
				Patient.	Controls.		
					1	2	3
1	1	Unidentified	Throat	2	0	0	2
1	2	Unidentified	Stool	10	0	2	7
1	3	B. coli	Stool	20	0	0	14
1	4	Strep. non-hem.	Stool	2	0	3	3
2	5	Pneumococcus	Throat	0	10	0	3
2	6	Strep. non-hem.	Throat	0	11	0	3
2	7	Strep. non-hem.	Throat	0	0	10	0
2	8	B. coli	Stool	0	12	30	3
2	9	Strep. non-hem.	Stool	0	10	0	3
3	10	B. coli	Stool	10	4	8	5
3	11	Staphylococcus	Stool	0	10	0	5
3	12	Strep. non-hem.	Stool	0	0	0	0
4	13	Strep. non-hem.	Throat	7	0	0	8
4	14	Strep. non-hem.	Throat	17	6	6	8
5	15	Strep. non-hem.	Throat	0	0	0	7
5	16	Strep. non-hem.	Throat	6	12	0	5
5	17	Strep. non-hem.	Tonsil	3	5	3	6
5	18	Strep. non-hem.	Tonsil	3	5	3	6
6	19	Strep. non-hem.	Stool	15	17	15	27
6	20	B. coli	Stool	35	47	37	52
6	21	Strep. non-hem.	Throat	5	10	20	12
7	22	B. coli	Stool	20	15	6	25
7	23	Strep. non-hem.	Throat	3	10	0	0
8	24	Strep. non-hem.	Throat	3	0	4	4
8	25	Strep. non-hem.	Throat	0	0	0	10
9	26	Strep. non-hem.	Tooth	0	12	4	0
9	27	Strep. non-hem.	Tooth	0	12	0	0
10	28	B. coli	Stool	7	4	7	8
11	29	Staphylococcus	Stool	0	0	0	0
11	30	Strep. non-hem.	Throat	0	0	7	5
11	31	Strep. non-hem.	Throat	0	0	8	6
12	32	Strep. non-hem.	Throat	3	0	3	0
12	33	Strep. non-hem.	Throat	3	0	0	0
13	34	Strep. non-hem.	Throat	0	0	4	5
14	35	B. coli	Stool	22	37	15	0
14	36	Strep. hem.	Throat	0	7	0	0
14	37	Strep. non-hem.	Throat	22	32	10	5
15	38	Strep. non-hem.	Throat	0	5	0	3
16	39	B. coli	Stool	25	30	8	20
16	40	Strep. non-hem.	Stool	10	4	10	8
17	41	B. coli	Stool	20	5	20	3
17	42	Strep. non-hem.	Throat	30	5	0	30
18	43	B. coli	Stool	0	0	5	3
18	44	Strep. non-hem.	Throat	0	0	3	0
19	45	B. coli	Stool	0	0	0	27
19	46	Strep. non-hem.	Tooth	5	0	0	11
20	47	B. coli	Stool	19	15	0	21
20	48	Strep. non-hem.	Stool	0	0	10	0
20	49	Strep. non-hem.	Stool	0	12	20	5
20	50	M. catarrhalis	Throat	32	25	27	28
20	51	Strep. non-hem.	Throat	0	8	21	0
20	52	Strep. non-hem.	Throat	0	10	0	11
20	53	Strep. non-hem.	Tooth	0	0	0	5
20	54	Strep. non-hem.	Tooth	0	0	0	4
21	55	Strep. hem.	Throat	5	5	19	10
21	56	Strep. non-hem.	Throat	5	5	0	5
21	57	B. coli	Stool	5	5	11	26
21	58	Strep. non-hem.	Stool	0	5	10	20

TABLE 1.—RESULTS OF SKIN TESTS WITH VACCINES IN ARTHRITICS AND CONTROLS.—(Continued.)

Case number.	Vaccine number.	Strain.	Source.	Diameter of reaction in mm. at 24 hours in:			
				Patient.	Controls.		
					1	2	3
22	59	B. coli	Stool	20	17	25	10
22	60	Strep. non-hem.	Stool	15	5	15	0
22	61	Strep. non-hem.	Stool	20	0	0	5
22	62	Strep. non-hem.	Throat	15	5	0	0
22	63	Strep. hem.	Throat	16	6	8	5
22	64	Unidentified	Throat	10	0	5	0
23	65	M. catarrhalis	Throat	10	22	17	15
23	66	Strep. non-hem.	Throat	0	27	5	0
23	67	Strep. non-hem.	Tooth	0	0	0	6
24	68	Strep. non-hem.	Throat	0	3	8	5
24	69	B. coli	Stool	0	3	0	0
25	70	B. coli	Stool	27	0	7	6
25	71	Unidentified	Stool	15	10	6	5
25	72	Strep. non-hem.	Stool	0	0	6	0
25	73	Strep. non-hem.	Throat	0	0	7	4
26	74	Strep. non-hem.	Throat	0	3	4	0
27	75	Strep. non-hem.	Tooth	8	0	23	0
27	76	Strep. non-hem.	Tooth	10	0	15	0
27	77	B. coli	Stool	15	20	35	25
28	78	B. coli	Stool	27	27	17	0
28	79	M. catarrhalis	Throat	50	35	40	4
28	80	Strep. non-hem.	Throat	15	5	5	0
29	81	Staphylococcus	Throat	0	5	0	10
29	82	Strep. non-hem.	Throat	0	0	0	0
29	83	B. coli	Stool	0	4	8	10
30	84	B. coli	Stool	8	5	0	17
30	85	B. coli	Stool	15	17	8	22
30	86	Strep. non-hem.	Throat	5	6	0	0
31	87	Staphylococcus	Throat	25	5	27	10
31	88	Strep. non-hem.	Throat	22	0	2	0
32	89	Strep. non-hem.	Throat	7	13	3	6
32	90	Strep. non-hem.	Throat	5	5	2	3
32	91	Strep. non-hem.	Throat	14	6	2	3
32	92	Strep. non-hem.	Stool	5	0	0	4
32	93	B. coli	Stool	27	20	5	35
32	94	Strep. non-hem.	Tonsil	25	5	23	12
32	95	Strep. non-hem.	Tonsil	11	3	20	6
33	96	Strep. non-hem.	Throat	0	3	0	0
33	97	Strep. non-hem.	Throat	0	3	0	0
33	98	B. coli	Stool	0	5	0	27
33	99	Strep. non-hem.	Stool	0	0	0	9
33	100	Strep. non-hem.	Stool	0	0	0	0
34	101	Strep. non-hem.	Tooth	0	2	5	0
34	102	Strep. non-hem.	Tooth	5	2	4	0

Even in an acute disease like typhoid fever from the second week on, the blood usually possesses a strong bactericidal effect. In pneumococcal infections, to which Solis-Cohen refers repeatedly, the normal bactericidal effect of the blood usually persists for several days after the onset of the pneumonia.<sup>15</sup> Furthermore, in pneumonia patients with persistent foci of infection remaining after the healing of the pulmonary process, the development of the bactericidal property of the blood is not retarded.<sup>16</sup> We can see, therefore, that the examination of the bactericidal property of the blood may

be misleading, even in pneumococcic infections and that until direct evidence is brought forward showing that this method usually gives good results in diseases of known etiology, indirect evidence in obscure conditions is of little value.

We also regard with skepticism the results obtained by skin testing the patients with vaccines made from different bacterial strains cultivated from various sites. The specificity of a skin test can be established only by testing a strain on a large number of controls as well as on the patient. Reactions obtained with controls have usually not been examined in the skin tests thus far reported.

The interpretation of skin sensitiveness is simple in such diseases as tuberculosis, glanders, and certain fungus infections where a strong, specific sensitivity develops, but the interpretation of slight skin reactions is usually impossible. Such procedures as skin reactions with concentrated urines (Wildbolz<sup>17</sup> reaction) and with horse serum (Busacca<sup>18</sup> reaction) in tuberculosis were once believed to be specific enough to be used for diagnostic purposes. The effect of non-specific irritation, *e. g.*, the application of cantharides plaster, shows regular variations in the course of different infectious diseases.<sup>19</sup> Such observations must warn us not to accept without due criticism the specificity of a skin reaction. The determination of the etiologic relationship between a disease and a certain bacterium is usually a very difficult task and the history of bacteriology shows that assumptions made on an insufficient basis have usually proven false.

At this point, we would like to present our own experience with skin reactions, the study of which, beside their eventual application to vaccine therapy, appeared of interest because rheumatoid arthritis presents certain characteristics suggesting that allergy may play an etiologic rôle. Skin reactions usually have a wider zone of specificity than serologic reactions and so offer better chances for finding strains to which the patients are markedly sensitive. By controlling the skin reactions carefully by tests on several other subjects, we obtained essentially negative results. We shall give, therefore, a short description of them only in regard to the claims which have been offered that with the help of skin tests it is possible to obtain useful information in both the etiology and therapy of rheumatoid arthritis.

The technique used for preparation of the vaccines was as follows: Cultures were obtained on blood agar plates and in broth, and several strains of the different bacterial species were isolated on blood agar plates. The vaccines were made from cultures on plain or chocolate agar slants. The bacterial emulsion was standardized with the help of a barium sulphate suspension and, after heating for 1 hour between 58° and 60° C., 0.3 per cent tricresol was added. Skin tests were usually made with 0.05 cc. of the vaccine on the forearm of the patient and the three controls.

In all, 102 vaccines, obtained from bacteria isolated from 34 patients, were examined. Forty-seven vaccines were made from strains isolated from the throats of the patients. Of these, 36 were non-hemolytic streptococci (alpha and gamma types), the rest various throat organisms. Forty-one strains were isolated from stools, with 23 identified as *B. coli* and 14 as streptococci. Ten streptococcus strains were isolated from extracted teeth and 4 from excised tonsils. Four hundred and eight skin tests were made with these vaccines.

The results, as shown in Table 1, were essentially negative, as very few of the patients gave skin reactions which would indicate specific hypersensitiveness. A few strains (Nos. 61, 62, 64, 80, 88) gave definitely positive reactions (1 cm. or more), while all 3 controls gave insignificant tests. But a larger number (23) gave very slight reactions on the patients from whom they had been isolated, while at least 1 control gave a definitely positive reaction. We might expect this, according to the laws of chance, since the controls outnumbered the patients 3 to 1. One patient (Case 22) who reacted more strongly to 3 of the 5 above-mentioned "positive" strains, reacted to a whole series of streptococcus strains more strongly than most of the subjects tested, as well as to a colon bacillus strain. This patient was possibly hypersensitive to the *Streptococcus viridans*, although her stronger reactions may not have been specific at all. Another patient (Case 31) who reacted more strongly to his own streptococcus strain than the controls, reacted also to another streptococcus in the same way. A third patient (Case 2), who was tested with 5 autogenous and 21 heterologous vaccines, constantly gave negative (19 out of 26 (83 per cent)) or very slight reactions (average diameter 0.2 cm.). A non-specific fluctuation of the irritability of the skin and possibly a sensitization to certain bacterial groups would seem to account for the variation in the strength of the skin reactions.

Another interesting finding was that certain bacterial species, regardless from whom isolated, tended to give large reactions. This is illustrated by the table below, where the results obtained with *B. coli* and *M. catarrhalis* are compared with the strains of non-hemolytic streptococci from throats and stools.

TABLE 2.—SKIN REACTIONS WITH DIFFERENT ORGANISMS.

Strain.	Source.	Number of tests.	Per cent 1 cm. or more.	Average diameter in millimeters.
<i>B. coli</i> . . . . .	Stools	92	52	13.0
<i>M. catarrhalis</i> . . . . .	Throat	12	92	23.0
<i>Streptococcus non-hem.</i> . . . .	Throat	144	16	4.5
<i>Streptococcus non-hem.</i> . . . .	Stools	56	27	5.0

This striking difference was most likely due to what may be called the natural toxicity of the bacterial species concerned.



As half of our controls were patients with arthritis, our observations allow no conclusion as to the presence of hypersensitiveness to *Streptococcus viridans* in arthritic patients. The majority of patients gave slight or no reaction to the relatively large doses of vaccine which we used. However, if we take the group of arthritics as a whole, whether controls or not, 24 per cent showed reactions greater than 1 cm. in diameter and 10 per cent 2 cm. or greater. In comparison, 17 per cent of the non-arthritic gave reactions 1 cm. or more and only 3 per cent 2 cm. or greater. Myers *et al.*<sup>20</sup> concluded that patients with rheumatoid arthritis gave stronger reactions to nucleoproteins of *Streptococcus scarlatinae*, whereas Derick and Fulton<sup>21</sup> discovered only slight differences with nucleoproteins from hemolytic and green streptococci in comparing normals with an arthritic group of unspecified type. MacKenzie and Hanger,<sup>22</sup> using derivatives of hemolytic and green streptococci, found no relationship between positive skin reactions and any one disease or group of diseases.

From our results and those cited above, we feel that there is certainly no allergy to streptococci as shown by skin reactions present in the arthritic patient comparable in strength to the allergy developing in tuberculosis and certain other chronic infectious diseases. One of the authors (C. L. S.) after repeated skin tests on himself, developed a marked skin reaction to *Streptococcus viridans*, giving stronger reactions than any of the patients. In those diseases where allergy plays an important rôle, the allergy developing in the disease is usually much stronger than the allergy developing after vaccination.

**Summary and Conclusions.** 1. Skin tests made with bacterial strains isolated from arthritic patients do not allow us to select specific strains for vaccine therapy.

2. Skin tests without using several subjects as controls are without any significance.

3. Variations in the skin reactions may be explained by differing irritability of the patient's skins, natural toxicity of the bacterial species, or possibly by a sensitization to certain bacterial groups.

4. The different methods which have been recommended for the selection of specific vaccine strains are without a solid theoretical or experimental foundation.

5. The above conclusions suggest that the therapeutic effect, if any, gained from autogenous vaccines is non-specific.

6. The hypothesis that rheumatoid arthritis is a disease of allergic origin is not supported by conclusions drawn from the interpretation of uncontrolled skin reactions with autogenous vaccines.

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## SPECIFIC TREATMENT OF SEPTIC INFECTIONS, PARTICULARLY WITH AID OF BACTERIOPHAGES.\*†

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THE temporary invasion of the blood stream by infectious micro-organisms is doubtless of frequent occurrence and in malaria, relapsing fever, typhoid fever or lobar pneumonia it may present no particular reason for alarm. However, when a positive blood culture shows *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus hemolyticus* or *Streptococcus viridans*, the vision of a fatal septicemia comes even to the optimistic physician. Many of these patients might have escaped such a grave complication if their infection had received adequate attention while still a localized disorder before invasion of the blood stream. A considerable part of regional surgery is directed to forestall just this catastrophe by providing external drainage or local antiseptic treatment of the infected region.

Unfortunately, it seems to me, there has been a relative neglect of specific bacteriologic diagnosis in some of these local surgical conditions. American surgeons are, in general, aware of the need for a gross and microscopic pathologic study of tissues which they remove from the patient, but as yet seem not to sense fully the

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importance of a bacteriologic study of inflammatory lesions and exudates. The therapeutic measures of drainage and chemical disinfection are not uncommonly assumed to apply with equal efficiency to all such lesions, so that specific recognition of the microbic parasite is considered to be a superfluous refinement. All will grant the value of knowing when an abscess contains bacilli of anthrax or of bubonic plague or of gas gangrene, but these infections are so unusual with us that we take the chance. I wish to plead the importance of specific diagnosis in the more common inflammatory exudates and wound infections, the importance of recognizing such common microbic parasites as the staphylococci, the streptococci, the various types of pneumococci, the hemoglobinophilic bacilli of Pfeiffer and of Ducrey and the Klebs-Loeffler bacillus. Efficiency in treatment of the patient can hardly suffer because of accurate knowledge of this kind and not infrequently it may be helpful to know the specific nature of the infectious agent.

This is emphatically true when one wishes to employ a specific antiserum as against the diphtheria bacillus or against a particular type of pneumococcus or against a streptococcus. It is also emphatically true when one attempts to employ such specific lytic agents as the bacteriophages. These peculiar bacteriolytic agents<sup>1</sup> act efficiently against only particular bacterial species and sometimes only against particular varieties within the species. The early specific bacteriologic diagnosis and the early application of the therapeutic measures effective against that specific type of infection either alone or in conjunction with proper local incision, excision and chemical disinfection may often suffice to ward off the danger of septicemia. On the other hand not inconsiderable numbers of septicemias are recognized subsequent to local surgical incision or excision undertaken without due regard to and often without previous recognition of the nature of the infecting microbe.

When the local inflammatory lesion is associated with a temperature reaching 103° F. or higher on 2 or 3 days or presenting marked sudden temperature elevations associated with rigors and rapid depressions associated with diaphoresis, one should not hesitate too long before subjecting the blood to a microscopic and a cultural examination. The blood count and malaria search are commonly asked for, but it is really astounding to observe the period of septic fever which may sometimes be recorded on the bedside chart, even in some of our large hospitals, before a blood culture is made. Perhaps the physician may excuse his inaction here by a desire to avoid frightening the patient or perhaps because he himself does not wish to know the truth on account of his generally hopeless outlook in septicemia. For this latter attitude I see no defense. As for frightening the patient, the taking of blood for culture may be readily camouflaged and even a physician patient may be misled to think that the specimen is being taken for chemical analysis, sero-

logic test or for careful and elaborate matching of blood for transfusion. In general, however, there is no real need for deception and the patient himself will often manifest a keen interest in his blood culture without fully sensing its grave significance.

During the last few years my associates and myself have been particularly interested in a study of the possible value of bacteriophages in the treatment of septic infections and in an attempt to learn how to use these agents so that they may be helpful. Given a bacteriophage which will completely destroy the bacterial culture in the test tube, it is easy to hope that it may be equally effective in eradicating the same bacteria from the body of the infected patient. In this we have been doomed to disappointment. The interaction between bacterial growth and specific bacteriophage is evidently subject to wide variations and influenced by many environmental factors. Temperature, acidity<sup>2</sup> or alkalinity of the medium, presence of blood, blood serum<sup>3</sup> or inflammatory exudate and the presence of an antiseptic chemical may be sufficient to impede the lytic action of the bacteriophage and permit the overgrowth of the bacteria even in the test tube. In the body of the patient some of these agents, as well as others still unrecognized, may be expected to interfere. In fact by a logical consideration of the results of experiments in the test tube one may quite reasonably arrive at the conclusion that no bacteriophage effect can be expected to occur in the living body.<sup>4</sup> This conclusion has its supporters just as there are enthusiasts of the opposite extreme opinion.<sup>5</sup> Actually, however, the matter cannot be settled by argument and discussion. Clinical trial, subject to many inaccuracies, must nevertheless furnish the final answer as to the value of bacteriophage therapy.

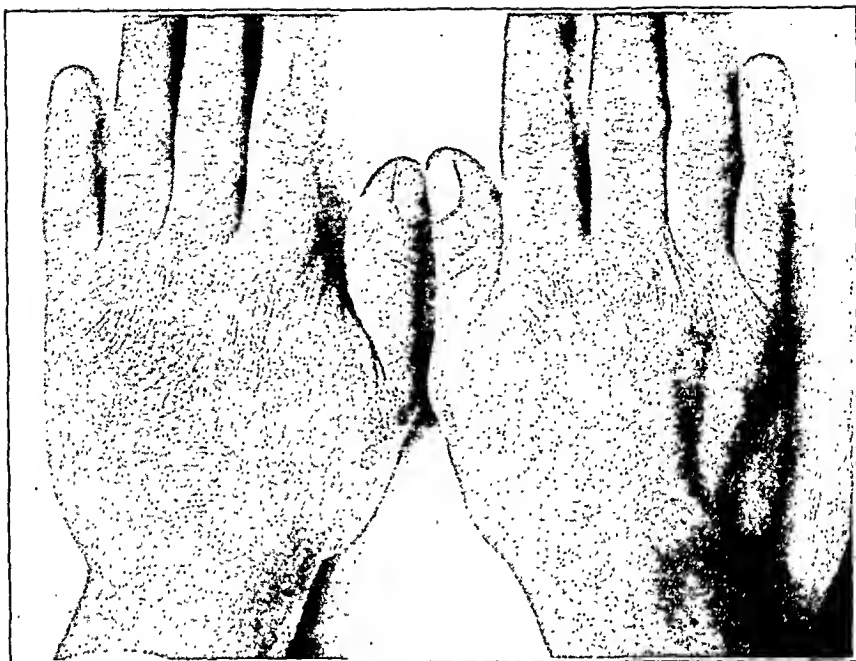
My colleagues and I have had the opportunity to observe the clinical application of bacteriophages in a considerable number of patients and have been privileged to prepare the bacteriophages and carry out the laboratory procedures for a great many more. We have come to feel that the antistaphylococcus bacteriophage, made in a broth medium for local application and in an asparagin medium for injection into the tissues or into the circulating blood, has already been established as a valuable therapeutic agent, not only in local staphylococcus infections, as in wounds, boils,<sup>6</sup> carbuncles and osteomyelitis, but also in staphylococcus bacteremia.<sup>7</sup> Our enthusiasm for this agent has not diminished at all with continued experience in its use. When the local lesion is easily accessible it is well to irrigate it with the bacteriophage and to apply the latter as a wet dressing. Injections are also made into the tissues about the margin of the lesion and, in case of a boil, injection through a very fine needle into the base of the lesion may be employed to wash out the pus through a small opening at the center. At the same time subcutaneous injections should be given at a distant site, about twice

a week, as a vaccine. When the lesion is deeply situated, as in actively progressive osteomyelitis, abscess of kidney or multiple early abscesses of the lungs, the intravenous injection is the method of choice. In staphylococcus bacteremia, the intravenous treatment is now invariably recommended and employed by us, together with application of bacteriophage locally if the primary lesion is superficial or easily reached. In these patients after a preliminary blood culture, we begin with a small dose, as a rule, 0.5 cc. of undiluted asparagin bacteriophage, or preferably 5 cc. of a 1 to 10 dilution of this, intravenously. After 40 min. 1 cc. of the undiluted preparation is given and after another 40 min. 2 cc. This procedure is continued, doubling the dose each time until one reaches the dose of 8 or 16 cc. or until the patient presents the signs of a shock reaction. We have given in this way as much as 70 cc. intravenously within 24 hr. and we have record of 1 patient, a child, who received 140 cc. within 24 hr. without serious effect. In most patients, however, a definite reaction will appear fairly early, often after a total amount of 3.5, 7.5 or 15.5 cc. has been given. Approximately 25 to 35 min. after an injection the patient goes into a chill which may be severe. It is well to be ready with warm external applications and with oxygen for the relief of dyspnea and cyanosis. The internal temperature rises rapidly and at the end of a chill of 20 to 30 min. it is usually between  $104^{\circ}$  and  $106^{\circ}$ . Sweating and rapid fall in temperature to  $99^{\circ}$  or below follow in an hour or so and the temperature begins to rise again after about 12 to 20 hr. We regard this reaction as favorable. The patient who fails to react will sometimes have yielded a sterile blood culture immediately before the injections were started. On the other hand the patient in whom the blood culture is positive tends to develop this shock reaction. If he does not, the outlook is in our experience unfavorable.

After the reaction, small intravenous injections of bacteriophage, 1 to 4 cc., should be continued daily for several weeks, even though the blood culture has become negative. Neglect of this has, in some instances, been followed by undesirable metastatic abscess. However, there is a possibility that too prolonged bacteriophage therapy may be associated with progressive emaciation.

Localized purulent lesions should receive appropriate surgical attention, but one can afford to be far more conservative in the use of excision and incision than he would be in a staphylococcus infection not receiving bacteriophage. The experienced surgeon who deals with a few of these patients quickly recognizes the difference in behavior and modifies his surgical technique to meet the new situation.

In one instance we have treated a purulent collection, situated in a bursa on the back of the left hand over the fourth and fifth metacarpals, by immobilization and aspiration and irrigation with bacteriophage through the needle and later by irrigation through one



A



B

FIG. 1.—Hands of L. S., photographed March 29, 1933. The site of most severe earlier inflammation is indicated by the thickened skin. On March 6, 1933, the patient presented himself with a fluctuating prominence surrounded by swollen red area covering the dorsum of the left hand. Aspiration obtained thick hemorrhagic pus which, on culture, yielded *Staphylococcus aureus*. On March 8 the cavity was again aspirated and irrigated 6 times with bacteriophage, being left in the collapsed state. This treatment was repeated on March 10 and 13. On March 15 the cavity was punctured with two needles and washed through with 6 cc. of asparagin bacteriophage. This treatment was repeated on March 16, 17, 18 and 20. The fingers were fixed by wooden splint until March 18, but after that time free movement was permitted. Cultures of the thin exudate obtained on March 20 remained sterile. The patient also received immunizing dose of 1 cc. bacteriophage into the deltoid region on March 6, 10, 15, 22 and 25. He remained at work all the time and the functional result has remained perfect.

needle with outlet through a second larger needle. At first the cavity yielded thick blood-tinged pus showing *Staphylococcus aureus* on culture. The last aspiration yielded a minute drop of pink fluid, cultures of which remained sterile. The hand has healed without incision, scar, disability or deformity (Fig. 1).

Osteomyelitis is a frequent sequel of staphylococcus bacteremia, particularly in young persons. Intravenous bacteriophage therapy is useful in limiting the extension of the process during the earlier stages and local applications of bacteriophage after surgical drainage are helpful in promoting favorable progress. In collaboration with orthopedic surgeons, particularly Albee,<sup>8</sup> Carter and Gratz, we have had opportunity to become wholly convinced of the value of bacteriophage in staphylococcus infections of bone. As an example of this type of infection a brief summary of a case which terminated in death after a period of 4 months is presented. The clinical chart for this period is so extensive that its reproduction has been deemed inadvisable.

**Case Report.**—M. H., schoolgirl, aged 17, developed osteomyelitis of the right innominate bone, beginning on December 16, 1932. This extended to involve the entire ilium, part of the ischium and the hip joint. There was also serous arthritis of the right knee and a rounded spot of rarefaction in the upper right tibia. Her first operation was performed on December 28 at another hospital. Upon admission to this hospital on January 19, she was desperately ill. Blood culture taken soon after admission yielded four colonies of *Staphylococcus aureus* per cc. of blood. That evening the soft parts over the hip were incised and a small amount of the diseased bone removed. Cultures were inoculated from the exudate. At the same time a transfusion of 200 cc. was given. The next morning it was possible to recognize colonies of staphylococcus in the cultures from the diseased tissue. At the request of the surgeon, Dr. C. M. Gratz, bacteriophage treatment was begun. A dose of 1 cc. antistaphylococcus asparagin bacteriophage was given intravenously and 12 cc. of the broth preparation of the same was injected into the single rubber drain. On January 21, the growth in the blood culture of January 19 was first recognized and it was decided to push the intravenous treatment to a shock reaction. A blood culture was taken, which remained sterile, and then at 11 A.M. the series of intravenous bacteriophage injections was begun, 2, 4, 8 and 10 cc. being given at 11 A.M. 12 noon, 1.22 and 2.45 P.M. respectively, the total amount being 24 cc. The chill began at 3.52 P.M. and lasted 22 min. and the temperature rose to 106 at 4.15 P.M., quickly falling to 99 at 8 P.M. On January 22 and 23 the dose of intravenous phage was 4 cc. on each day and after that 2 cc. daily to January 28. The broth preparation was injected into the drain daily. The patient did well. Her temperature remained below 102° except on January 25 and 26, following a transfusion on January 25.

On February 20, under ether anesthesia, the plaster dressing was completely removed, the wound was revised, position of the right lower extremity changed, the right knee joint aspirated and a new extensive plaster dressing applied over vaseline pack, with two rubber catheters left in the wound, one with its opening within the capsule of the hip joint and the other in contact with the ilium. These catheters were brought out through the anterior part of the plaster. Dependent counter drains were left extending posteriorly through the buttock. The knee joint was left closed and the aspirated fluid gave negative cultures. The tibia was not incised. The

plaster dressing, however, was carried all the way down to include the toes of the right foot and the ankle of the left foot.

The patient did not do so well after this operation. Blood culture taken the next day gave delayed positive growth of staphylococcus in one broth flask while a second flask and three plates remained sterile. On February 24 the drainage from the wound yielded abundant colonies of colon bacilli and some hemolytic streptococci. Anticolon bacillus bacteriophage was therefore added to the staphylococcus phage put into the two drains on February 27. Now hemolytic streptococci and the bacillus of green pus appeared in abundance on the cultures from the exudate and on March 2 the antipyocyaneus bacteriophage and our feeble antistreptococcus phage were called into play. However, there appeared a marked dermatitis, suggesting erysipelas, on the skin visible beneath the upper margin of the plaster dressing and it was considered unwise to withhold the streptococcus serum. The concentrated streptococcus serum of the New York State Department of Health was injected, at first in small intracutaneous and subcutaneous doses and then in larger intramuscular doses, 20,000 units on each of 4 days, March 4, 5, 6, and 7. Subsequently, urticaria and vomiting complicated the clinical picture. The intravenous staphylococcus phage was continued, as also the mixture of 3 or 4 broth phages into the drains. Nutrition became a problem and emaciation progressed. Hormone injections, eschatin and insulin, were used in the hope of a favorable influence. Blood cultures on February 28, March 23, April 6 and 15 remained negative. Eventually on April 14 the vomiting became so persistent that the patient was becoming dehydrated, with acetone breath and acetone in the urine and pitiable emaciation. The intravenous bacteriophage dosage was now reduced and after April 16 it was discontinued. Glucose salt solution was given intravenously on April 15 and 18, and on April 18 a duodenal tube was passed through the nose for forced feeding. This tube remained in place until the morning of April 22, by which time the patient had visibly gained flesh and strength and was again able to take food in the natural way and to retain it.

Meanwhile the hip had become fixed and much of the plaster dressing had been cut away. The patient could be turned onto her side and onto her face without pain and it was possible to remove and renew the padding under the plaster.

On April 24, under avertin and nitrous oxid, the dressings and drains were removed, roentgenograms were made which showed favorable progress of the bone lesions, and the wounds were distended and dressed and a new plaster dressing applied. Following this there was again persistent vomiting and the duodenal tube was again introduced on April 27. The posterior drainage opening were revised and enlarged on May 2 and 3 and the exudate revealed predominant hemolytic streptococci. Streptococcus serum was given, 60,000 units from May 4 to May 6 and saline irrigation to the drains was substituted for bacteriophage mixture, as the latter was not effective against streptococcus. Progressive emaciation, intractable diarrhea and a terminal aspiration pneumonia continued to death at 1.40 A.M., May 17. Necropsy was not permitted.

This case illustrates the influence of the staphylococcus bacteriophage, even though the patient did not survive. The infection of the blood stream was overcome and the lesions in right tibia and right knee joint receded without surgical drainage. In the ilium and the hip joint, secondary infection with other bacteria, particularly streptococci, appeared to be responsible for the ultimate failure.



Blood stream infection with the streptococci is one of the common types of septic infection. The hemolytic streptococcus extends from primary lesions in nose, throat, ear or uterus into the walls and lumina of altered veins and eventually into the circulating blood. Up to the present time we have had no success in our attempts to apply the bacteriophage phenomenon to the treatment of such conditions. On the other hand we are convinced that the vigorous efforts to improve the quality of antistreptococcus serum obtained

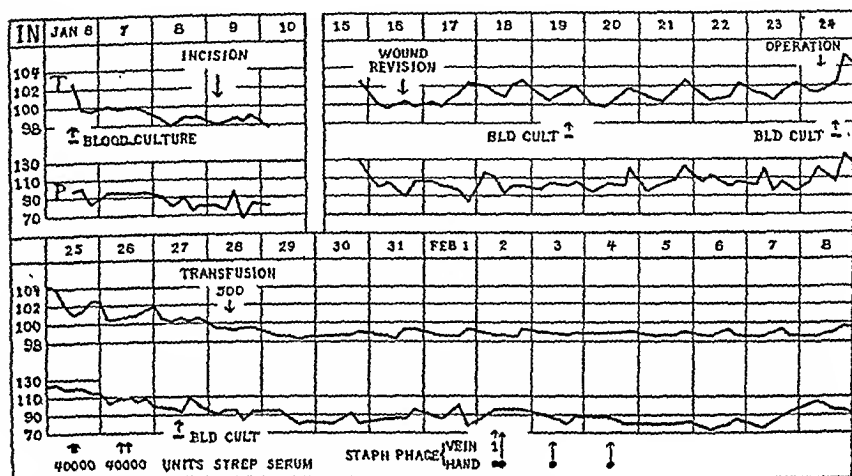


CHART I.—Abridged record of I. N., a student nurse aged 20, who had chapped hands on January 1, 1933, and on January 5 a severe throbbing pain in the left hand extending up above the left elbow. On the morning of January 6 the hand was dressed by a surgeon and subsequently the patient vomited and became unable to remain on duty. She was admitted to the hospital at noon with diagnosis of furuncle and complicating cellulitis. Blood culture taken on admission remained negative. She was discharged on January 10 and again admitted as patient on January 15. On January 24 the left axilla was incised by Dr. John F. Erdmann and a second large purulent collection on the right side of the neck was opened. In both these regions there was abundant hemorrhagic pus. The aid of specific treatment was at once requested by Dr. Erdmann. The axillary and cervical pus contained abundant streptococci, but no staphylococci. Concentrated streptococcus serum of the New York State Department of Health was given on January 25 and 26, a total of 80,000 units, and a transfusion on January 28. Improvement was prompt. The hand, however, was not doing so well and here the exudate contained staphylococci. A single intravenous dose of asparagin staphylococcus bacteriophage was given on February 2 and wet dressing of the broth phage was applied on February 2, 3 and 4, with prompt healing.

from immunized horses have, in recent years, succeeded in the production of serum really potent against these streptococci. So far we have had a few successes in frank septicemias treated with such serum and we have observed some remarkably quick recoveries, after use of the concentrated experimental antistreptococcus serum of the New York State Laboratory, in streptococcus infections of the hands with lymphatic extension to form axillary abscesses, particularly in physicians, nurses and in laboratory personnel (Chart I).

Endocarditis lenta, with vegetative lesions on the valves of the

heart and persistent *Streptococcus viridans* in blood culture, is a chronic septicemia, which has engaged our attention for some years. Our attempts to apply the bacteriophage phenomenon<sup>9</sup> in treating this disease have been followed by some diminution of our self assurance as well as death of our patients. However, the field has not been abandoned.

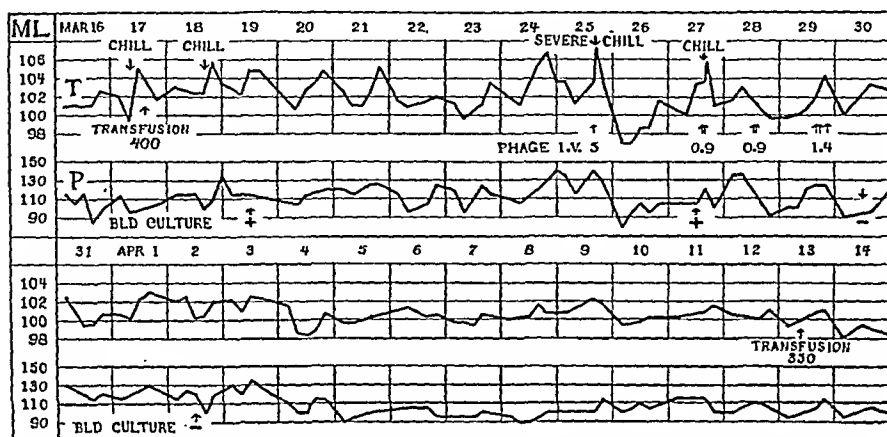


CHART II.—Abridged record of M. L., white female aged 21, admitted March 15, 1931, suffering from pelvic thrombophlebitis and colon bacillus septicemia following abortion about March 1 and curettage about March 3. This patient has been mentioned in some of our previous papers but the clinical record has not been previously presented. Blood culture on March 19 yielded colon bacilli and this organism was found susceptible to lysis by bacteriophage available in the laboratory. However, its use was not invited until the temperature had reached 106.8° on March 24 and the condition was considered hopeless. It was decided to begin with a series of intravenous injections of the asparagin preparation spaced at 40 min. and the initial dose of 5 cc. was given about 4.30 P.M. on March 25. The shocking reaction which followed within  $\frac{1}{2}$  hr. prevented further injections. After a chill lasting from 4.50 P.M. to 5.20 P.M., the temperature reached 107.2° at 5.20 P.M. This was followed by profuse diaphoresis and apparent collapse which continued until noon of the next day. The expected exitus failed to take place and on March 27 after taking a blood culture we were bold enough to start again with an intravenous dose of 0.5 cc. at 3.05 P.M. followed by a second dose of 0.4 cc. at 3.42 P.M. Just as the arm was being prepared for the third dose at 4.15 P.M. the patient went into a rigor which lasted until 4.26 P.M. when her temperature was 105.8°. On March 28 two more intravenous injections were given, 0.5 cc. at 1.35 P.M. and 0.4 cc. at 2.10 P.M., without evident reaction, and on March 29, 3 intravenous injections, 0.5 cc. at 4 P.M., 0.4 cc. at 5.40 P.M. and 0.5 cc. at 8.15 P.M. No further bacteriophage was administered. Blood cultures, taken on March 30 and on April 2, remained negative.

On April 3, after a fit of coughing the patient complained of pain in the chest and upon physical examination and roentgenologic study a right spontaneous pneumothorax was discovered. The lung was compressed except near the diaphragm where it was held by a thick adhesion. Apparently there was an old tuberculous process here. With rest in bed the lung expanded again and the pneumothorax disappeared. On April 13 she was transfused with 350 cc. of blood at 9.30 A.M. On April 22 the patient was allowed out of bed and on April 28 she was discharged from the hospital. Her right leg remained slightly larger than the left as a sequel to the edema which had otherwise subsided. There was no other recognizable evidence of her illness.

Blood stream infection with paratyphoid and paracolon bacilli occurs in food poisonings and in the paratyphoid fevers without necessarily grave significance. Septicemia due to the colon bacillus,

however, seems to be more serious. It appears to come from ascending pyelonephritis and from septic wound infections and is frequently a terminal phenomenon, if one may judge by bacteriologic findings at early necropsy. We have employed bacteriophage in the treatment of 3 septicemias due to colon bacilli and have supplied the bacteriophage for treatment of a fourth patient in this category in another hospital. The anticolon bacillus bacteriophage prepared in the asparagin medium was injected intravenously in all four. One died after repeated large doses without a very definite reaction and with persistent positive blood culture. Another patient with a septic thrombosis of the pelvic veins following abortion suffered a frightful shock from the first intravenous dose of bacteriophage, reacting with a chill and temperature rise to 107.2°. She made a complete recovery (Chart II). In the other 2 patients the reactions were mild, the septicemia disappeared but the infection of the urinary tract remained. One of these patients refused to bother with further treatment after her serious symptoms were relieved. In the other, the persisting infection of the urinary tract was complicated by pregnancy which had not been interrupted by the septicemia. However, 10 days after bacteriophage treatment had been discontinued the fever returned, followed, after 72 hr., by premature labor and the birth of a 6-months fetus which survived for an hour. Since then the patient has become clinically well but the urine still contains pus cells and numerous colon bacilli.

The use of bacteriophages in the treatment of localized colon-bacillus infections, such as those of the urinary tract, external wounds and intestinal lesions has been found distinctly helpful in a large proportion but not by any means in all the cases. Rather elaborate laboratory studies are required in order to select the most promising among the bacteriophages for each particular infection and to get ready the most effective preparation of the bacteriophage selected. Unfortunately the colon bacilli are not always found susceptible to lysis by the races of bacteriophages in our possession. However, when it is possible to get a bacteriophage fully potent against the particular colon bacillus and to employ it with intelligence and skill, its therapeutic value compares well with that of the staphylococcus bacteriophages in their therapeutic field.

**Comment.** The summarized records of 4 patients here presented have been selected to illustrate some of the ways in which we have attempted the specific treatment of infection. The cellulitis and bursitis of the hand illustrated in Fig. 1 was not a desperate condition. The technical procedure of irrigation was tried on this patient with the idea that we might later use a similar principle in treating a purulent pericarditis or a purulent arthritis. The other 3 patients have been selected because they appear to illustrate a favorable influence of specific treatment by bacteriophages or by serum in

patients very seriously ill. Unfortunate cases with early fatal termination have not been included in the brief series here discussed and it is hoped that no one will be deceived by this omission. Such fatalities will be found recorded in the more detailed publications from our laboratory.

It will be observed that we have not relied exclusively upon serum or upon bacteriophage but have employed these agents in conjunction with, and as aids to, other therapeutic measures. Furthermore the nature, variety and quantity of clinical material which has become available for our experimental therapy has not permitted setting aside untreated controls. Many of the moribund patients might be left to make such a control group but this would not be fair nor justified either as scientific or humanitarian. The present purpose is not, therefore, to present proof that the use of specific serum or of specific bacteriophage decides the issue between life and death in human beings. In fact we assume that such proof will not be required by the sympathetic observer and cannot at present be furnished in sufficient strength to convince the unsympathetic skeptic. There can be no doubt, however, that these agents are capable of causing changes in the condition of the patient and in the course of his disease. Knowledge of their action, care and skill in their use, coupled perhaps with good luck, may sometimes contribute to the fortunate outcome of an illness otherwise without good prognosis.

In conclusion, I would say that effective therapeutic application of bacteriophages, as well as effective use of therapeutic serums, requires an intimate and sympathetic coöperation between the workers at the bedside and the workers in the laboratory, most perfectly realized when the same persons consult together in both places, studying together the behavior of the patient and the behavior of the cultures. The use of commercial preparations of bacteriophages leaves much to be desired in this particular respect and is not free from other important objections.<sup>10</sup> In general the attempts at wholesale commercial exploitation of these agents is, in our opinion, to be deprecated at the present time.

**Summary.** 1. The early specific diagnosis of infectious disease by immediate application of the appropriate bacteriologic technique is strongly urged.

2. Specific diagnosis facilitates proper care of the patient and isolation of the specific microbe makes possible the intelligent selection of specific serum or specific bacteriophage.

3. The appropriate application of antistreptococcus serum or of bacteriophages against the staphylococcus or the colon bacillus requires intimate collaboration of clinician and laboratory worker. The use of these agents is recommended as beneficial to some patients suffering from infection with the respective microbes.

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## THE RACIAL FACTOR IN PERNICIOUS ANEMIA: A STUDY OF FIVE HUNDRED CASES.

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ALTHOUGH it has been the impression of clinicians for some years that pernicious anemia is a disease for the most part confined to the temperate zones and more particularly North America, the British Isles and Northern Europe, there has been doubt in the minds of some that race plays a definite rôle in the distribution of the disease. It has been suggested that patients from various parts of the different continents are attracted to centers where they are more likely to receive the best treatment in the hands of certain highly trained clinicians and, for this reason, the incidence of many other diseases as well as pernicious anemia is relatively higher in regions around these particular centers.

The first satisfactory statistical evidence in favor of definite racial discrepancies in the incidence of this disease appeared in 1921 as a result of a clinical study of 150 cases of pernicious anemia by Levine and Ladd.<sup>1</sup> An analysis of their group study indicated a lower frequency among Italians, Russians, Jews and immigrants from Eastern Europe as compared with a definitely higher percentage of cases among North Americans, Canadians and immigrants from Ireland, England, Sweden and Denmark.

The purpose of this survey is to confirm as far as possible the sug-

gestive findings of the above mentioned authors with a larger group of cases, employing the statistical data obtained from a study of 500 case histories of patients with typical pernicious anemia.

Information concerning this subject in the better known textbooks and systems of medicine is meager. French,<sup>2</sup> Bunting<sup>3</sup> and Cabot<sup>4</sup> found no restriction of the disease to any particular nationality. McCann and Maitland-Jones<sup>5</sup> remark the high incidence among the white race, particularly those of Nordic origin. Panton, Maitland-Jones and Riddock<sup>6</sup> in a clinical analysis of 117 cases of pernicious anemia noted that all were of English descent with the exception of 1 German and 6 Hebrews. Montgomery<sup>7</sup> studied a group of 320 cases occurring in patients from the Canadian provinces of Alberta, Saskatchewan and Manitoba and found, despite the inhabitation of these areas by a large French, Belgian and German population, practically all of his patients were blonds of Anglo-Saxon and Scandinavian heritage except for 2 Germans and 1 Pole. Cornell<sup>8</sup> states that it has been recognized for some time that Michigan, Ontario, New Brunswick and the eastern township of Quebec show high rates of incidence. This author quotes figures showing the high mortality rates for this disease in the United States, Denmark, Sweden and the Canadian provinces of British Columbia, Nova Scotia, Quebec and Ontario up to 1924. Binswanger<sup>9</sup> reviewed 230 cases occurring between the years 1900 and 1926 finding no difference in the morbidity in Germany, Austria and Switzerland. No outstanding racial tendency was observed other than that Hebrews comprised a very small number of the group and that the disease incidence was greater in Sweden and Finland than in Germany.

The rarity of pernicious anemia in North American negroes has long been recognized. Cornell<sup>8</sup> quotes Longcope that the disease seldom, if ever, affects full-blooded negroes. Carr<sup>10</sup> reported an incidence of about 5% in a group of 134 cases. Willson and Evans<sup>11</sup> reported 8 mulattoes in a clinical study of 111 cases. Jamison<sup>12</sup> found 54 cases of pernicious anemia among 122,524 admissions for all causes to the Charity Hospital in New Orleans during the period 1920 to 1926; of these 12 (29%) were negroes, a rather high figure considering the low incidence of the disease among the white race in the South.

Of 256 patients with the disease in the Cook County Hospital from 1921 to 1926 Traut<sup>13</sup> found an unusually large number of Scandinavians and Poles. During the period of this study about 33% of the total admissions were colored, but only 8 of these had the disease. Matthews<sup>14</sup> emphasizes the low incidence among negroes with the statement that only 28 cases are to be found reported in the literature up to 1929. Of 4940 total admissions to the United States Veterans' Hospital in Tuskegee, Alabama, during a 5-year period ending in 1928, only 2 negroes were diagnosed as

having the disease. Pernicious anemia in natives of tropical and oriental countries is extremely uncommon according to Morris,<sup>15</sup> Mills,<sup>16</sup> Yang and Keefer<sup>17</sup> and Williams.<sup>18</sup>

Mortality statistics, reported by Mills,<sup>19</sup> show the death rate from this disease to be definitely higher in Ireland, Scotland, Canada, England, Wales, United States, Norway, Netherlands, New Zealand and South Africa as compared with Italy, Uruguay, Barbados, Nigeria, the Philippines, Hawaii, Straits Settlements, Iceland, Haiti, and Ceylon. In the United States this author finds the mortality high in the areas centering around the Great Lakes Region and Northern California and a comparable area in Europe embracing the British Isles, Netherlands, Denmark and Northern Germany. Recently, Sturgis and Isaacs,<sup>20</sup> in a group of 580 patients, noted the incidence to be significantly greater in English-speaking people and Scandinavians than in immigrants from Russia, Italy and Eastern Europe.

**Analysis of Peter Bent Brigham Hospital Data.** From April, 1913, to November, 1932, 80,415 patients were admitted to this hospital for all causes, among which over 500 cases were diagnosed as pernicious anemia. For the purposes of this study 500 cases exhibiting only the typical manifestations of the disease were chosen.

FIG. 1.—TABULATION OF DATA.\*

	All countries.	United States.	Total foreigners.	Russia.	Canada.	Ireland.	England.	Italy.	Scotland.	Germany.	Greece.	Sweden.	Denmark.	Miscellaneous.	Negro.	All foreign countries except Canada, Ireland, England, Sweden, Denmark and Scotland.
Total admissions . . . . .	80,415	47,203	33,212	7559	7157	6272	2814	2332	1593	1206	1126	965	160	2025	4503	14,251
Per cent of total admissions . . . . .	100	58.7	41.3	9.4	8.9	7.8	3.4	2.9	1.9	1.5	1.4	1.2	0.2	2.7	5.6	17.9
Total number of P. A. cases . . . . .	500	291	209	14	81	47	25	4	7	5	0	12	2	9	3	32
Per cent of P. A. cases . . . . .	100	58.2	41.8	2.8	16.2	9.4	5.0	0.8	1.4	1.0	0	2.4	0.4	1.8	0.6	6.4
Per cent of P. A. cases among total admissions from various countries . . . . .	0.62	0.61	0.62	0.18	1.1	0.74	0.88	0.17	0.43	0.41	0	1.2	1.2	0.44	0.06	0.22

\* These figures include all admissions up to November, 1932.

An examination of Fig. 1 shows the compilation of data as essentially similar to that employed by Levine and Ladd.<sup>1</sup> In view of the fact that the hospital discontinued the statistical tabulation of the birthplaces of all admissions shortly after 1921, it has been necessary to use these authors' figures (see Fig. 1, horizontal column 2) for computing the total admissions from a given country, with the exception of the figures for negroes, who comprise slightly

over 5% of all admissions and may all be considered as American born.

Certain striking differences in incidence become apparent on closer analysis of the figures in horizontal columns 2 and 4. While 9.4% of all admissions were Russian born, only 2.8% of the pernicious anemia patients were Russian and all of these, except 1, were Hebrews. Conversely, 8.9% of all admissions were from Canada, yet 16.2% of the pernicious anemia cases were Canadian. In other words, the total admissions from both of these countries were approximately equal, 7559 Russians and 7157 Canadians, but there were only 14 Russians with the disease as compared to 81 Canadians.

Similar discrepancies may be pointed out between England and Italy. Whereas 2.9% of the total admissions were Italian born and 3.4% English, only 0.8% of the pernicious anemia patients were Italian as compared with 5% English immigrants. The same contrast is apparent between Italy and Sweden; with  $2\frac{1}{2}$  times as many Italians as Swedes, there were only 4 of the former but 12 of the latter with the disease.

These differences are more strongly emphasized by reference to the last vertical column in Fig. 1 in which all admissions from foreign countries are tabulated, exclusive of those in which the disease is more prevalent, *i. e.*, United States, Canada, Ireland, England, Scotland, Sweden and Denmark. There were 14,251 (17.9%) of the total admissions from the countries not so excluded, yet only 32 (6.4%) of the pernicious anemia patients were from these countries. In contrast, 66,164 of the total admissions were from the United States, Canada, Ireland, England, Scotland, Sweden and Denmark and 465 (93%) of the pernicious anemia cases were from these countries, excluding negroes. The percentage of pernicious anemia patients from Eastern and Southern European countries is therefore 6.4% as compared with 93% from the 6 countries previously mentioned and the United States; about 14 times more prevalent in the latter group.

Fig. 2 illustrates in graphic form the data in the last horizontal column of Fig. 1, namely, the ratio of the number of patients with pernicious anemia born in a given country to the total number of admissions to the hospital for all causes from that country. The contrast here again is quite striking and it is readily seen that the majority of the patients with the disease were from Sweden, Denmark, Canada, England, Ireland and the United States, and, to a lesser extent, Scotland and Germany.

Of all the patients admitted to the hospital during the period of this survey, 0.61% had pernicious anemia, yet over 1% of all the patients from Canada, Sweden and Denmark and over 0.7% of those from Ireland and England had the disease as compared with 0.18% of those from Russia (all Hebrews except one), 0.17% from Italy, 0.06% negroes and 0.22% from miscellaneous countries.



Among the last group were 1 Lithuanian, 1 Latvian, 1 Frenchwoman, 1 Pole, 1 Portuguese, and 2 Hebrews born in Austria.

The familial factor in pernicious anemia has been definitely established (Meulengracht<sup>21</sup>). Moreover, it is the opinion of many that there is a definite constitutional factor involved in the hereditary aspect of this disease (Draper,<sup>22</sup> Cornell,<sup>8</sup> Barker,<sup>23</sup> Conner<sup>24</sup> and Davidson and Gulland<sup>25</sup>). In the light of these views, one may add the clinical impression that not only does the disease occur with greater frequency in the white races of temperate zones, but that

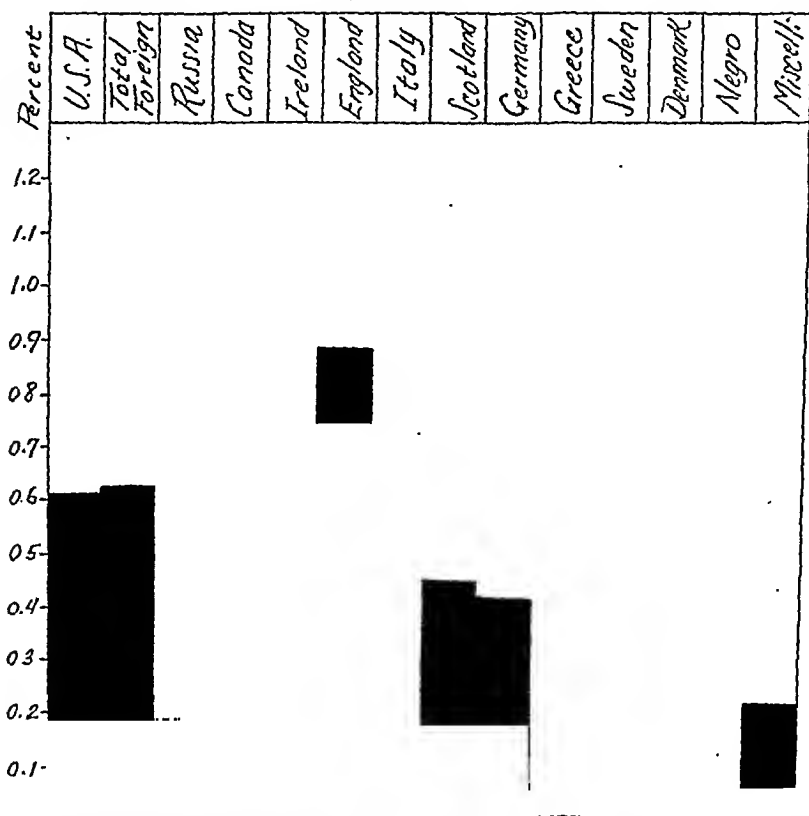


FIG. 2.—Per cent of pernicious anemia cases among total admissions from various countries.

among these people the ones affected in the vast majority of instances are the light complexioned, fair-haired type. This opinion is corroborated by Murphy<sup>26</sup> in a large series of patients at this clinic, and even in those cases where the disease occurred in dark-complexioned or heavily pigmented individuals, it has been possible to obtain a history of fair-complexioned ancestors or siblings in practically every case. It is of added interest to note that Erulkar<sup>27</sup> has remarked the occurrence of pernicious anemia in light-haired individuals in India.

The following brief résumés are recorded as striking evidence of

the importance of pigment or its absence in relation to susceptibility to the disease:

H. M. (Med. No. 36862). A young Portuguese woman, aged 24, with very dark skin, dark brown hair and gray-blue eyes gave the following family history:\* Her maternal great-grandfather was exceptionally light-complexioned and although he had jet-black hair he had been considered as "one of the whitest men who had ever lived in the Azores." The maternal grandmother was 1 of 6 children, all of whom were so light-complexioned that they were known in their particular community in the Azores as the "white family." Two of the maternal grand-uncles adopted the name of "White" when they left the Azores to come to the United States, and their children, who now live in Massachusetts, bear the proper name of "White." The maternal grandmother was very fair, with light hair and blue eyes. The patient's mother, however, was quite darkly complexioned, with black hair but fair skin. There was one brother who was quite fair and had light brown hair, yet, who, as a child, was a distinct blond with golden hair. There was another brother and a sister with very dark complexions and a sister with very fair skin. These people had always considered themselves full-blooded Portuguese.

C. P. C. (Med. No. 32239). A 52-year-old Italian woman with reddish hair and brown eyes afforded the following information: Her father and mother were both born in Milan, Italy, and were fairer than the average Italian. Numerous members of the family were of the blond type and there were blond and fair-haired members on both sides. Her father and mother both had brown eyes and black hair. Of two paternal aunts one had black hair and the other blond. There were 13 siblings in the mother's family, 2 of whom had red hair. The patient stated that some of her own children "might have been taken for Swedes," 2 of her 3 sons having blue eyes and blond hair.

L. L. D. (Med. No. 38258). A 49-year-old negress stated that her mother was a white Canadian woman and that one of her brothers died at the age of 62 of a disease called pernicious anemia.

The evidence just presented is in favor of the view that the predisposition to this disease is racial in character as well as constitutional and familial. It is largely confined to those individuals endowed with a diathesis characterized by a fair complexion, light hair, blue eyes and achlorhydria. Of the 500 cases investigated there were only 66 in which the color of the irides was recorded and of these 72.7% were blue, 16.7% brown and 10.6% shades of blue. It is felt that these characteristics are definite components of the genotype in such individuals who, under the influence of certain so-called releasing factors in their environment, as yet undetermined, may eventually suffer a loss of the intrinsic factor of Castle<sup>28</sup> and develop pernicious anemia.

Although unrelated to the general trend of this paper, the following data are recorded as worthy of mention: Of the 500 cases studied during this survey, 274 entered this hospital over a 13-year period terminating in 1926, *i. e.*, prior to the advent of liver therapy and 226 were admitted during a period of 6 years after the advent of liver therapy. Although the absence of accurate follow-up records precludes an exact knowledge of the total mortality in both of these groups, it is definitely known that over 60% of the first

\* As obtained by Dr. Marshall N. Fulton of the Peter Bent Brigham Hospital.

group are dead and very likely most, if not all, of this group have died, whereas only about 11% of the latter group have died. Definite knowledge is at hand, however, concerning 51 autopsied cases, 36 of which were performed before 1926 and 15 during the following 6 years.

The average age at death of the first group was 51 years, that of the latter 58 years; whereas the average length of life after the onset of the disease in those patients not receiving liver was 30 months, it was 29 months in the group dying after the advent of liver treatment.

The decline in the mortality due to pernicious anemia was predicted by McKinley<sup>29</sup> in 1929 and mortality statistics from Toronto<sup>30</sup> covering the period from 1923 to 1931 show a substantial lowering of the death rate due to pernicious anemia since the discovery of liver therapy. This, of course, is undoubtedly the unpublished opinion of many others. The very fact that there are so few fatalities in this group since 1926 is sufficient proof that liver therapy prolongs the lives of patients with pernicious anemia.

Observations among this series of cases concerning the causes of death in the autopsied cases indicate that those patients who received optimum liver therapy with a corresponding return of their blood to normal figures died of conditions essentially unrelated to pernicious anemia. The only possible exception to this is the type of patient who develops progressive neurologic disease in the face of adequate treatment. This has been previously intimated by Zadek<sup>31</sup> and Diebold<sup>32</sup> with regard to patients dying in spontaneous remissions and by Fahr<sup>33</sup> in patients dying during significant remissions following liver therapy.

In this series of 51 autopsied cases, 36 of the patients died prior to the advent of liver treatment with an average antemortem hemoglobin of 29% and 1,320,000 red blood cells per cmm. Of these, 29 died of circulatory failure and intercurrent infections as a result of the debilitating effects of anemia, 3 died of circulatory failure complicated in one instance by a chronic pachymeningitis and leptomeningitis, in another by acute hemorrhagic pachymeningitis and in the last by active tuberculosis of the hilar lymph nodes; 3 died of sepsis and another of acute tuberculous bronchopneumonia.

Fifteen patients came to autopsy after the advent of liver therapy, 10 of whom were inadequately treated as evidenced by an antemortem red cell count of 1,870,000 and hemoglobin of 39%. Six of this group died of circulatory embarrassment and intercurrent infection; in the remainder death was due to vascular accidents terminated by bronchopneumonia. The remaining 5 cases showed an average antemortem hemoglobin of 81% with an average red cell count of 4,500,000. Three of these patients died of circulatory accidents, 1 showing multiple thrombi in the pulmonary arteries and veins, another thrombosis of the right pulmonary artery and 1 thrombosis of the left coronary artery, all terminating in bron-

chopncumonia. Of the remaining 2, 1 died of a staphylococcus septicemia and 1 of carcinoma of the gall bladder with extension to the liver, and terminal bronchopneumonia.

Of the total number of cases autopsied, 10 had chronic fibrous pleurisy, not proven tuberculous; 9 showed evidence of healed, apical, non-clinical pulmonary tuberculosis, 2 had active hilar lymph-node tuberculosis and 1 died of acute tuberculous bronchopneumonia. These findings are worthy of note in the light of a recent study by Barron,<sup>34</sup> who believes there is a definite antagonism between pernicious anemia and tuberculosis.

Opinions have varied from time to time concerning the sizes of the liver and spleen in pernicious anemia. In this particular group, however, there was no difference in the size of the liver in those patients autopsied prior to or since the advent of liver therapy, the average weight of the liver in the whole group of 51 cases being 1598 gm. On the other hand there was an appreciable diminution in the size of the spleen in the 15 patients dying after 1926, the average weight being 171 gm. as compared with 234 gm. in the group not treated with liver. This is in accordance with the belief of some that, clinically, the spleen, in adequately treated cases, is less likely to be enlarged and possibly diminishes in size after the institution of specific therapy.

**Summary.** Evidence derived from a study of 500 cases of typical pernicious anemia is presented to confirm the opinion that pernicious anemia is a disease largely confined to the white race in temperate zones and that among these people there is a definite racial, as well as constitutional, predisposition, the latter being embodied in individuals endowed with a diathesis characterized by fair complexion, light hair and light-colored eyes.

An analysis of 51 cases of proven pernicious anemia, 36 autopsied prior to and 15 since the advent of liver therapy, indicates that the causes of death of those adequately treated in this latter group are not directly related to the anemia and are essentially conditions met with in ordinary people of the same age.

The weight of the spleen in patients autopsied before the advent of liver treatment was greater than in those dying after 1926, the weight being 234 gm. in the untreated group as compared with 171 gm. in the latter group. There was no change in the weight of the liver in either group, the average being 1598 gm.

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## OBSERVATION ON THE PRACTICAL SIGNIFICANCE OF VENOUS PRESSURE IN HEALTH AND DISEASE WITH A REVIEW OF THE LITERATURE.

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In a previous communication we attempted to describe a relatively inexpensive apparatus and simple technique for the determination of venous pressure according to the original direct method

of Moritz and Tabora. It is now our purpose to demonstrate its clinical application and usefulness in the hands of the general practitioner who daily is confronted in his patients with diagnostic problems in cardiovascular disease.

The literature reveals the fact that many investigators have studied the problem of venous hypertension from many angles, employed many techniques, and pointed out its significance in practically every pathologic state of the vascular system. Consequently, we realize that our subject is not a new one. On the other hand, it is our impression that most of this work has been from the standpoint of research, wherein not only hospitalization of the patients studied but also elaborate and expensive apparatus have been required. It has naturally followed, therefore, that the problems studied and the conclusions reached have been of interest only to physiologists, cardiologists and research investigators. Our experience, however, has convinced us that the information gained from venous pressure determinations in numerous disease entities can be extremely useful and interesting, not only to the internist practising in large clinics, but also to the general practitioner in the smaller communities, once his interest and curiosity are aroused, and he finds he has another simple diagnostic guide at his finger tips.

**Normal Venous Pressure and Its Physiologic Variations.** There are four fundamental functional factors affecting peripheral venous pressure; namely: (1) *Vis a tergo* or heart action; (2) intrathoracic pressure; (3) hydrostatic level; (4) volume of blood in the vein. Physiologic fluctuations in any one of the above is reflected in altered venous tension within its normal range.

The normal venous pressure has been reported by different authors as varying from 50 to 150 mm. of water. In Table 1 are listed the normal ranges as determined by various investigators:

TABLE 1.—NORMAL RANGES OF VENOUS PRESSURE.

	Water. mm.		Water. mm.
Moritz and Tabora <sup>1</sup> (1910)	100	Gonezy, Kiss and Enyedy <sup>3</sup>	120
Schott <sup>2</sup> (1912)	130	Criep <sup>6</sup>	102
Villaret, St. Girons and Jacquemin-Guillaume <sup>3</sup>	130	Eyster and Middleton <sup>7</sup>	110
Bedford and Wright <sup>4</sup>	50-150	Conradi <sup>8</sup>	80-130

Needless to say, the fact that different techniques have been used will necessarily account for some of the apparent discrepancies in the normals arrived at by different investigators. Based on our own and the findings of others, we have accepted a range of 60 to 120 mm. of water as normal for subjects at rest in the supine position; readings above 140 and below 40 we believe are always pathologic.

According to Criep<sup>6</sup> there is an increase in venous pressure with age up to 35 years, and then a decrease to 50. This increase and decline remains within normal limits, however.

Venous pressure rises with exercise,<sup>4</sup> and during exercise there is

a slight secondary fall as increased cardiac output results from increased venous load.<sup>9</sup> For this reason patients should be at rest for some time (at least 15 minutes) before a reading is taken.

No definite relationship has been found to exist between arterial and venous pressure according to our observations. Bedford and Wright<sup>4</sup> came to the same conclusions, and Crippe,<sup>6</sup> while stating that there is a general tendency for venous pressure to drop as systolic pressure rises above 115 and to rise with diastolic pressure, finally decides that no constant relation can be determined.

We have found that the pressure in the femoral vein, with the patient at rest in the supine position is usually from 10 to 40 mm. higher than pressure in the arm veins of the same patient—perhaps due to mechanical pressure effects within the abdomen. We are not inclined to attach much importance to this difference unless the pressure in the femoral exceeds 140 mm.

Evans<sup>10</sup> states that obesity raises the venous pressure due to pressure on the veins by fatty tissue. Conversely, emaciation lowers venous pressure.

**Venous Pressure in Cardiac Decompensation. I. Diagnosis.**—It is accepted that the output of the heart is determined by the venous load put upon it. An increase in the load on the normal heart up to a point results in an increased output. Cardiac failure is defined by Eyster<sup>11</sup> as "that condition in which the venous pressure exceeds the range within which the heart is capable of responding, by increased work, to increased venous load." This increase in load, with failure, can occur in either the right or the left heart or both. We are able to measure the load on the right heart, but at present no means is available for measurement of the intrapulmonic pressure, which determine the load on the left heart.<sup>2</sup>

A distinction should be drawn here between right and left sided heart failure. Clinically the usual types of decompensation involve the right heart alone or a combination of the right and left hearts. Here the venous pressure is raised in the greater circulation, and can be measured quantitatively. Rarely one meets with cases of cardiac failure involving only the left heart. Here the venous pressure is raised in the lesser circulation (where we are unable to measure it) and the venous pressure in the greater circulation is not affected until the right heart also gives way. Any further reference hereafter to cardiac failure will mean failure including the right heart.

In *cardiac failure*, whether of primary or secondary origin, venous pressure is always elevated.<sup>6, 7, 10, 17</sup> Furthermore, such venous hypertension antedates the clinical signs and symptoms of failure by several hours, at least.<sup>11, 16, 18</sup> In view of these facts it will be seen that venous pressure readings in cases of suspected or impending heart failure may well prove a valuable therapeutic and diagnostic aid to the clinician.

In *pneumonia*, where the usual signs of congestive failure are difficult to recognize because they are obscured by the signs of respiratory embarrassment, venous pressure readings are of extreme value. In fact, Kastlin and Maelachlan<sup>16</sup> state that venous pressure, rather than the classic arterial tension, is the delicate prognostic and diagnostic criterion in pneumonia when the state of the circulatory system is the crux of the situation. Cardiac failure can invariably be positively diagnosed, if present, in the course of pneumonias when venous pressure readings are made routinely.

Venous pressure has also been of value in *differential diagnosis*. As there is no rise in this pressure in cases of allergic asthma, pneumoconiosis, emphysema and chronic pulmonary fibrosis, we have a valuable aid in differentiating the dyspnea and cyanosis due to these conditions from that caused by acute right heart failure.<sup>10</sup> In cardiac decompensation, the venous tension usually varies from 140 to 300 mm. of water, with values of 160 and upward in cases of acute failure. The pulmonary conditions named above usually show pressures from 60 to 120 mm., while allergic asthma cases often show pressures at the upper limits of normal, probably due to increase of intrathoracic pressure caused by increased expiratory effort.

In several cases of acute heart failure and of allergic asthma admitted as medical emergencies, immediate venous pressure determinations proved to be of tremendous value for us in differentiating the two conditions. In one instance the patient had received several 1 cc. injections of adrenalin outside, in a fruitless attempt to alleviate the symptoms. A venous pressure reading showed a hypertension of 240 mm. of saline, and venesection proved effective.

In cases of *pneumothorax*, unless enough collapse of lung tissue is present to cause dyspnea, no change in the venous pressure is found.<sup>10</sup> Similarly, in a case of bilateral pneumococcal *empyema* which we observed, the venous pressure remained normal throughout.

In *cerebral-vascular accidents* complicated by cardiac failure, the decompensation is at times overlooked because of the confusing chest signs which may be present. Such cases are more intelligently treated when the decompensation is recognized early by venous pressure determinations.

**II. Prognosis.** In the prognosis of cardiac failure, venous pressure determinations are valuable as to the degree and progress of the condition not obtainable by other means. Clark<sup>12</sup> was the first to set 200 mm. of water as the critical level in heart failure: above this level a further rise has unfavorable prognostic significance; a fall from this level lends a favorable outlook. Others have agreed with Clark.<sup>12</sup>

In pneumonia and other acute conditions in which cardiac failure may occur, the venous pressure readings—useful in diagnosis—



become doubly useful when prognosis is considered, since it is upon the sufficiency of the circulatory system that the final outcome often depends. Kastlin and MacLachlan<sup>16</sup> have shown that a persistently elevated venous pressure with a pulse rate above 120 usually foretells a fatal outcome. A low venous tension with a pulse below 120 makes for a good prognosis. In several of their cases, terminating fatally, arterial pressure remained normal during the course of the disease.

**III. Treatment.** Venous pressure readings in decompensated patients during therapy calculated to restore compensation will show, in cases reacting favorably to such treatment, a progressive return of venous pressure to normal.<sup>7, 10, 11, 12, 17, 19</sup> This level will be maintained as long as compensation lasts. Consequently it has been found practical to use venous pressure as an index to the efficacy of the treatment. During digitalization, readings are taken in a series spaced at 2- or 3-day intervals. After compensation is restored the intervals may be increased to weeks or months, as long as the patient is under observation. By this method it is relatively simple to detect early a beginning relapse into the decompensated state, the venous pressure elevation in cardiac failure occurring as mentioned above, before the clinical signs and symptoms become definite. Treatment may then be instituted at once and the heart muscle spared as much as possible.

Concerning venesection, the obvious step in right heart failure, from a theoretical standpoint, is artificially to remove some of the venous load on the heart by blood-letting. Unfortunately, in the past, this measure has generally been used as a procedure of last resort, more conservative treatment having failed. Such cases going on to a fatal outcome, venesection has been looked on with distrust if not with actual disapproval.<sup>16</sup>

Clark, in 1915, was the first to champion venesection when venous pressure rose above a critical level of 200 mm. of water. Recently other investigators have concurred in emphasizing the rationale of such a procedure and in deploring the fact that venesection is employed only in desperate cases where obviously any treatment would fail.<sup>6, 14, 16</sup> At a level of 200 mm. the patient is usually still in such condition that lost compensation, which digitalis and rest alone may not restore, will still respond favorably to the more radical procedure of venesection. This should be done in cases where the venous pressure is rising above the critical level, or remaining high, in spite of conservative treatment. In such cases at least 500 cc. or more of blood should be removed, as Meek and Eyster<sup>20</sup> have shown that at least this amount is required if any benefit is to be expected. Venous pressure readings are an index in these cases to the degree of immediate relief afforded the patient and, when taken in series, give information as to the duration of such relief.<sup>14</sup>

**IV. Venous Pressure Elevation Due to Localized Obstruction.** There are only two conditions causing venous pressure elevation: heart failure and obstruction to venous return. In the majority of cases of elevated venous pressure from local block, readings in different extremities will usually locate the obstruction. In one type, however, this does not hold true. Constrictive pericarditis, or *concretio cordis*, raises the general venous pressure at times regardless of whether it is postinfectious or idiopathic in origin. Many signs and symptoms are common to this condition and to cardiac failure, but the causative mechanisms are different. The essential defect in constrictive pericarditis is a limitation of diastolic relaxation of the heart caused by encircling bands of scar tissue, resulting in a low fixed stroke output of the heart. An excellent review of this condition is given by Burwell and Strayhorn.<sup>21</sup> In a case reported by these authors the venous tension reached 240 mm. and Volhard and Schmieden<sup>22</sup> report pressures up to 300 mm. In the 2 cases we have studied the pressures reached 240 and 265 mm. respectively. These pressures varied somewhat in different extremities and were of use in locating for the surgeon the main adhesive bands.

Although venous pressure readings are of diagnostic service in these cases, their greatest use is in evaluating the postoperative results of surgical release of constricting bands and adhesions. In our 2 cases referred to above, the venous pressures fell from 265 to 120 mm. in 1 case, and from 240 to 170 in the other, after surgery.

Evans<sup>10</sup> states that edema raises the venous pressure. As this occurs only in the part involved, readings in different extremities are of value in differentiating cardiac, renal and inflammatory edema. We have had no direct experience with this.

Evans also states that with ascites high venous pressures obtain in the legs. These return to normal with paraentesis. This we have found to be true in a certain group of cases where ascites is caused by portal vein block, as in portal cirrhosis. In 2 other cases studied we found ascites with elevated femoral pressure. Venous tension in the arm veins was normal or low. Paraentesis in each patient removed 4000 cc. of ascitic fluid, but the venous pressure in the femoral veins did not drop to normal. In 1 case it fell from 245 to 185 mm. and in the other from 225 to 170 mm. Further study, including exploratory laparotomy, revealed extensive peritoneal disease with many adhesions and enlargement of the mesenteric glands. In a 3d case, with elevation of femoral venous pressure and with evidence on physical examination of ascites, numerous attempts at paraentesis failed, presumably because of adhesions with loculation of fluid. Laparotomy here also revealed chronic peritoneal disease.

We have seen no reference in the literature to date regarding cases similar to the last three mentioned. While such a series is obviously too small for any conclusions, we believe the observations are worthy of further study and consideration.

**V. Venous Hypotension.** Search of the literature fails to reveal any reference to the pathologic significance of persistent venous hypotension. In the course of our investigations we have encountered several cases with such findings. A series of venous pressures taken over a period of time showed the venous pressure rising as the patients improved clinically. One such case was diagnosed carcinoma of the esophagus with cachexia and dehydration. The venous pressure was 20 mm. of water. One month after gastrostomy with regular feedings the venous pressure rose to 60 mm. (*i. e.*, normal). Another case of extrinsic carcinoma of the larynx with emaciation showed a venous tension of 10 mm. Both the clinical condition and the venous tension in this patient have remained unchanged.

A venous pressure reading on a case of acute coronary accident in the emergency ward revealed a pressure of only 5 mm. of water. The patient was confined to bed in the hospital over a period of 2 months. As he slowly convalesced, his venous pressure rose. At the time of discharge the venous tension was 94 mm. A similar case of acute vascular accident was observed in a patient who suffered a pulmonary embolus after appendectomy. The day following this accident the venous pressure was 40 mm. Over a period of 2 weeks his venous tension rose to 120 mm.

The above illustrations of venous hypotension are mentioned purely as suggestive; our observations are as yet too limited to serve as the basis for any conclusions. Possibly the cause for venous pressure in cachexia is in reduced blood volume and in reduced pressure on the venous channels.<sup>16, 17</sup> We have no explanation to offer for a fall in peripheral venous pressure in the acute vascular accidents, except the possibility of splanchnic shock, increasing the amount of blood in the splanchnic area at the expense of the peripheral circulation or of a lowered *vis a tergo* from the weakened myocardium, reducing pressure in the venous channels.

In regard to the meager literature on venous hypotension, it is interesting to note that Bedford and Wright<sup>4</sup> state that with the direct method of Claudé, which they used, it was difficult to measure accurately low venous pressure. Although we have had no experience with the indirect method it is possible the same criticism applies to it. With our apparatus, low venous tensions are as readily measured as higher pressures. It is to be hoped that the significance of venous hypotension will be more thoroughly investigated.

**Summary and Conclusions.** 1. With a simplified apparatus and technique at his command the general practitioner should find accurate venous pressure determination a practical diagnostic, prognostic and therapeutic guide in primary congestive heart failure and in other disease entities complicated by or simulating cardiac decompensation.

2. The use of venous pressure in various clinical conditions is herein discussed, with examples from our own experience.

3. The significance of venous hypotension has yet to be adequately investigated and furnishes another fruitful field for clinical research.

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## ARTERIOVENOUS FISTULA INVOLVING THE COMMON FEMORAL ARTERY IDENTIFIED BY ARTERIOGRAPHY.

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THE reasons for reporting this case are to illustrate the importance of definitely determining the site of an arteriovenous fistula by means of arteriography, and to demonstrate the clinical signs and symptoms of acquired arteriovenous fistula. This appears to be the first time arteriography has been used here in this type of case, and I had not seen similar reports in the literature at the time this case was originally reported.<sup>1</sup> Yater,<sup>2</sup> also, has referred to my original report as the first of its kind.

**Report of Case.** A youth, aged 19, was admitted to the clinic October 31, 1931, with bird shot wounds in both thighs. One shot had penetrated the upper third of the right thigh over the great vessels and painless swelling had followed immediately. Another shot had entered the anterior part

of the left thigh in the lower side, but had not caused swelling, or other symptoms (Fig. 1). Roentgenograms revealed 1 small shot in each thigh. Pulsations in the right femoral, right popliteal, right posterior tibial and right dorsalis pedis arteries were normal at the time of examination, and no bruit could be detected over the right thigh.

A compression bandage was applied over the swollen region of the right thigh. The patient was in the hospital under observation for 4 days, and during that time the swelling in the thigh gradually subsided. On the 6th day after the injury, a slight bruit could be heard over the femoral artery at the point where the shot had entered; at times the bruit was absent. A well-developed bruit, with thrill, was present 24 days after the injury over the upper third of the right thigh. The bruit was heard throughout



FIG. 1.—The points of entrance of the bird shot, 29 days after the injury. Enlargement of the lateral aspect of the right thigh is evident.

the cardiac cycle and was accentuated with each beat of the heart. When the right femoral artery was closed by digital pressure below the inguinal ligament, the apex beat of the heart decreased from 10 to 12 beats per minute.

November 24, determinations of oxygen content were made on blood removed from superficial veins of the right and left arms, right femoral vein, left femoral vein, and right femoral artery. The blood in each instance was withdrawn under oil without the use of a tourniquet, and the determinations of oxygen were made by the van Slyke gasometric method. The patient had been lying in a horizontal position for about 30 min. before the specimens of blood were withdrawn. The oxygen saturation of blood from the right arm vein was 57.2% by volume; from the left arm vein, 46.7; from the left femoral vein, 76.6; from the right femoral vein, 85.5, and from

the right femoral artery, 93.8%. Blood from the right femoral vein was bright red and was practically the same color as that from the right femoral artery. Blood from the left femoral vein was darker and corresponded more closely to the color of the blood removed from the arm veins than to that of blood from right femoral artery. Blood counts, urinalysis and the serologic test for syphilis gave negative results. Clinically, it was apparent that this patient had an arteriovenous fistula in the right thigh, probably involving one of the small branches of the femoral artery rather than the femoral artery itself.

July 8, 1932, an arteriogram of the right femoral artery was made by injecting into it 25 cc. of thorotrast. At the time the injection was made,

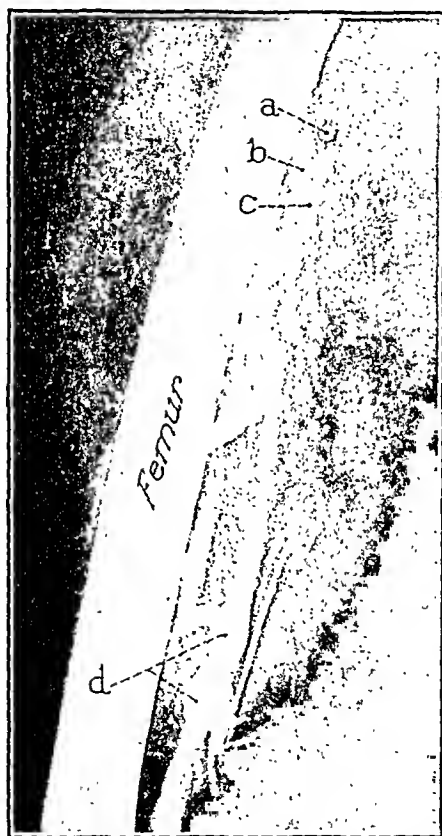


FIG. 2.—Arteriovenous fistula between femoral artery and vein; *a*, bird shot; *b*, femoral artery; *c*, femoral vein; *d*, saccular enlargements in the femoral vein.

the right femoral artery was closed by digital pressure just proximal to the site of injection. A series of films was made as quickly as possible. The patient experienced no ill effects from the procedure. The arteriogram revealed evidence of an abnormal communication between the femoral artery and vein (Fig. 2). The femoral vein was well outlined, indicating that the opaque medium had leaked from the artery into the vein by way of the fistula.

The patient was examined again March 24, 1933. The right thigh had become definitely larger than the left, a loud bruit could be heard over the entire thigh, and there was a marked thrill in the middle and upper thirds. The superficial veins were increased in size and number, as compared with

those of the normal left thigh. With the patient horizontal, the blood pressure of the left and right arms was 120 mm. Hg systolic and 70 diastolic, of the left thigh 120 systolic and 80 diastolic, and of the right thigh 140 systolic and 100 diastolic. When the right femoral artery was compressed just below the inguinal ligament, the apex beat of the heart dropped from 80 to 66 beats per minute. After the patient had been at rest for 20 min., the rate of the heart at the apex was 68 beats per minute. It dropped to 54 beats per minute when the right femoral artery was again closed by digital pressure. In a roentgenogram of the thorax the heart appeared to be of normal size. The cardiac output, as determined by the Grollman method, was 3.9 liters per sq.m. of body surface. This indicates a definite increase over the normal.

This case illustrates the importance of arteriography in determining the site of abnormal arteriovenous communications. With the history, the presence of a bruit and thrill over the right thigh and the bradycardiac reaction, the diagnosis of arteriovenous fistula of the acquired type seemed definitely established. The diagnosis was confirmed by the demonstration of a high admixture of arterial and venous blood in the right femoral vein. The site of the fistula could be determined only by means of arteriography, or by surgical exploration.

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### THE SYNDROME OF OBSTRUCTION IN THE LESSER CIRCULATION.\*

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IN this paper it is proposed to discuss a group of conditions which have in common the clinical features of cyanosis, dyspnea, polycythemia and right ventricular hypertrophy due to prolonged obstruction in the lesser circulation.

The oxygenating apparatus of the animal organism consists of an alveolocapillary wall set in between two distributing systems;

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on one side is the air with its life-sustaining oxygen, the necessary airways and respiratory pump of the suction type, and on the other is the blood with the oxygen-carrier hemoglobin, a distributing system of bloodvessels and the circulatory force pump, the heart. If one considers only the steps in the process of oxygenation, it will be noted that the respiratory system has but one responsibility, that of delivering to the necessary respiratory surface area oxygen in sufficient quantity and at adequate pressure to meet the demands of the organism. The circulatory pump, however, has two responsibilities. It must deliver to the opposite side of the alveolocapillary wall hemoglobin for the loading of oxygen, and then it must transport that oxygen and discharge it at the proper unloading stations throughout the body. Oxygenation is completed by the delivery of active oxygen to the cell. Anoxemia may be the result of a defect at any point in this apparatus, from the atmospheric reservoir of oxygen to the final unloading station at the level of the cell. At one extreme stands mountain sickness, at the other cyanid poisoning, in between are the various pulmonary and arterial conditions in which acute or chronic anoxemia of greater or less severity may be found. In Fig. 1 are shown the chief points at which obstruction in the "lesser circulation" may occur.

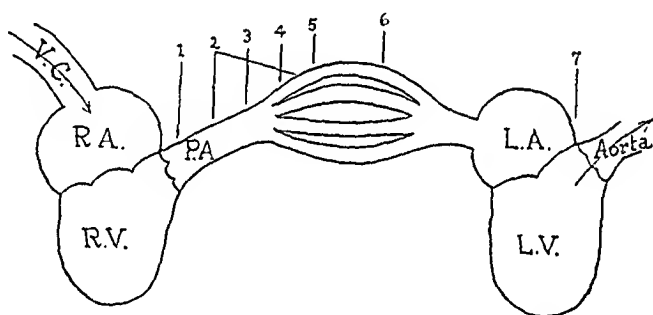


FIG. 1.—Diagram of lesser circulation showing most common causes of obstruction and their locations.

#### Obstructive lesions of the lesser circulation.

1. Congenital heart disease.
2. Pulmonary thrombosis and embolism.
3. Pulmonary arterial disease { Arteriosclerosis.
4. Pulmonary arteriolar lesions { Arteriolosclerosis.
- Inflammatory
- Syphilis.
- Rheumatic fever.
- Thromboangiitis.
5. Reduction of capillary bed.
  - Emphysema.
  - Pulmonary neoplasms.
  - Pulmonary tuberculosis.
  - Pneumoconiosis, etc.
6. Venous thrombosis.
7. Mitral stenosis.



The subatmospheric pressure in the chest not only keeps the pulmonary peripheral pressure low (the pressure in the pulmonary artery is only 20 mm. Hg), but assists the respiratory and circulatory functions of absorption, transportation and elimination of gases by its expansile effect upon the vascular bed and by its aspirating effect upon the blood. The anatomic evidences of this low pulmonary peripheral resistance are found on the one hand in the relatively small amount of muscle tissue normally present in the walls of the pulmonary arterioles, and on the other hand in the thinness of the right ventricle, normally 3 to 4 mm., as compared with a thickness of 12.5 mm. for the left ventricle, which works against a much higher peripheral resistance.

The primary effect of obstruction in the lesser circulation is to increase the blood pressure in the pulmonary artery; secondary effects are to produce anatomic changes in the pulmonary artery (arteriosclerosis) and in the right ventricle (hypertrophy). Secondary vascular changes may add to the obstructive effects of the primary lesion. The effect upon respiratory function is dependent upon the location, magnitude and *tempo* of the obstruction.

Because the pulmonary vein is remarkably free from disease, the only point beyond the capillaries at which obstruction is commonly found is at the mitral valve. The frequent association of pulmonary arteriosclerosis with mitral stenosis is generally ascribed to the heightened pulmonary arterial pressure. Since the primary obstruction at the mitral valve is beyond the pulmonary capillaries, the effect upon oxygenation is slight, until compensation fails.

The conditions in which we are particularly interested are those in which obstruction may be found anywhere from the right ventricle out to and including the pulmonary capillaries. Discussion will pursue the following plan:

I. Congenital cardiac defects of the cyanotic type.

II. Pulmonary thrombosis and embolism.

A. Experimental pulmonary thrombosis and embolism.

1. Partial occlusion of pulmonary veins.

2. (a) Ligation of a main branch of the pulmonary artery.

(b) Ligation of the main trunk of the pulmonary artery.

3. Pulmonary embolism.

B. Clinical illustrations of pulmonary thrombosis and embolism.

III. Sclerotic and inflammatory lesions of the small arteries and arterioles.

IV. Processes which affect primarily the capillary bed.

I. Congenital Cardiac Defects of the Cyanotic Type. The frequency of dyspnea, cyanosis, polycythemia and right ventricular hyper-

trophy in congenital cardiac defects in which there is a venous arterial shunt is too well known to justify extended discussion here. We confine ourselves to emphasizing the fact that precordial pain and syncope, two important symptoms common in congenital cardiac defects of the cyanotic type, were noted also in MacCallum's case of obliterative arteriolosclerosis and in Frothingham's case of extensive bilateral thrombosis of the small branches of the pulmonary arteries.

**II. Pulmonary Thrombosis and Embolism.** *A. Experimental Pulmonary Thrombosis and Embolism.* Obstruction of the lesser circulation has been produced experimentally in three different ways (Dunn,<sup>1</sup> Underhill,<sup>2</sup> Mann,<sup>3</sup> Binger *et al.*,<sup>4</sup> Schlaepfer,<sup>5</sup> Haggart and Walker<sup>6</sup>): (1) By ligation of a main branch of the pulmonary vein; (2) by partial or total constriction of the pulmonary artery itself; (3) by the embolic occlusion of smaller or larger branches of the pulmonary artery by the intravenous injection of paraffin, suspensions of potato starch or seeds of various sizes.

1. *Partial Occlusion of the Pulmonary Veins of One Lung.* This causes a prompt and a greater rise in pulmonary arterial pressure than when the pulmonary artery is partially ligated (Haggart and Walker<sup>6</sup>). At first the lung on the obstructed side shows great stasis and many hemorrhages in the alveoli. This exudate is slowly absorbed and replaced by a proliferation of connective tissue along the capillaries within the alveolar walls. After a year the fibrosis is well marked around the alveolar capillaries and around the medium-sized branches of the pulmonary artery (Schlaepfer<sup>5</sup>). In contrast, the lung on the unobstructed side shows early a physiologic and later a compensatory emphysema, but no connective-tissue proliferation in the alveolar walls. After a year the circumference of the pulmonary artery of the side not subjected to operation is larger than that of the other side.

2. (a) *Ligation of a Main Branch of the Pulmonary Artery.* Sauerbruch and Bruns<sup>8</sup> found experimentally that if a main branch of the pulmonary artery was ligated, fibrosis and shrinkage of the lung followed. In other words, a functionless lung is the result of sudden complete interference with its circulation. How much of the pulmonary arterial circulation may be cut off without anoxemia, the interrupted blood flow being detoured through other pulmonary channels along with the blood normally traversing them, we do not know. Much depends upon the condition of the myocardium and the state of the other lung. Experimentally, Haggart and Walker<sup>6</sup> found that clamping the left branch of the pulmonary artery for a period of time measured in minutes caused an immediate average, often only temporary, rise in pulmonary pressure of about 29 per cent, but that such a procedure brought about no significant variation in the size of the heart, heart rate or heart output. From 52 to 66 per cent of the pulmonary circulation could be cut off

without significant variation in the general circulatory condition of the animal. A critical point, however, was reached beyond which a circulatory collapse was precipitated by even a minute increase in the arterial obstruction. Dunn,<sup>1</sup> Binger<sup>4</sup> and others have found in experimental embolism a critical point of the same nature.

The results of these investigations may be summarized: Interference with respiratory function by grades of obstruction in the lesser circulation, comparable to what is often seen clinically, is easily demonstrable experimentally, but on account of great technical difficulties and the brief period of time that obstruction is applied in experiments on resting animals, the same cannot be said for the effects upon pulmonary arterial pressure and the right side of the heart. However, the clinical and pathologic evidences of heightened pressure and increased burden on the right ventricle are unmistakable.

(b) *Ligation of the Main Trunk of the Pulmonary Artery.* The pulmonary arterial pressure rises at once to an amount from 121 to 267 per cent of its previous level and then falls as the animal dies. The general systemic blood pressure falls sharply to one-third of the control level, the heart dilates, the minute volume shows a diminution of from 15 to 77 per cent and respiration becomes irregular and then stops.<sup>6</sup>

3. *Pulmonary Embolism.* Binger, Brow and Branch<sup>4</sup> say that the gross and microscopic pathology of lungs subjected to pulmonary embolism by the intravenous injection of starch suspensions is characterized by evidences of congestion, edema and atelectasis. These changes are associated with a reduction in lung volume, a decreased elasticity of the pulmonary parenchyma and a shallow tidal air. In 4 experiments on dogs they found the average arterial oxygen saturation before embolism 89.2 per cent and after embolism, 71.6 per cent. Following "seed" embolism, in which larger vessels are obstructed, these workers found a more marked arterial anoxemia than in "starch" embolism. In 12 dogs the average arterial oxygen saturation was 87.56 per cent before embolism and 62.68 per cent after embolism.

Binger, Brow and Branch<sup>4</sup> attribute the anoxemia of experimental pulmonary embolism to a "change in the quantitative relation of blood flow to the vascular diffusion area in the lungs. The nature of this changed relationship is twofold: (a) An increased rate of flow through the capillaries, the flow being so rapid that the blood cannot assume its normal load of oxygen; (b) a compensatory dilatation in the capillaries which are crowded with corpuscles in columns so thick as to interfere with the normal inward diffusion of oxygen."

Finally, as Dunn says, the results of all these investigations on obstruction in the lesser circulation must be weighed in the light of the knowledge that they were performed upon the "resting animal."

*B. Clinical Illustrations of Pulmonary Thrombosis and Embolism.*

Multiple thrombosis of the smaller branches of the pulmonary artery is not uncommon, but occlusion of a main branch is rare, and it is even more rare for the victim to survive long enough to show a secondary polycythemia from the effect of anoxemia on the bone marrow, and right ventricular hypertrophy from the prolonged effect of the increased burden on this side of the heart. Means and Mallory<sup>10</sup> have reported a case of this type. Their patient, a man, aged 60 years, showed marked dyspnea, cyanosis and swelling of the ankles. At a single examination the red cell count was not increased. On physical examination the lungs were notably clear. Congestive heart failure was the chief cause of death. At the postmortem examination both ventricles were much hypertrophied and dilated. The right ventricular wall was 7 mm. in thickness. The most important lesion, however, was complete thrombotic occlusion of the right pulmonary artery. "The pulmonary arteries beyond the point of thrombosis were entirely normal in appearance until the peripheral portion of the lung was reached, where many were found partially or completely occluded by fibrous plugs, typical in appearance of completely organized thrombi. Many of these showed canalization. It is particularly interesting that exactly similar lesions were found in peripheral portions of the left lung." The degree of organization of the clot suggested that it had been present for weeks, possibly months. A well-developed compensatory circulation through the bronchial artery and two other vessels which apparently originated from the inferior thyroid artery furnished additional evidence of the age of the obstruction. The reducing effect of the arterial occlusion upon the capillary bed is evidenced by the fact that the capillaries of the alveolar walls were difficult to make out, and very few red blood cells were found in the septa. Means and Mallory conclude with the statement that cyanosis and right-sided heart failure without other obvious cause may suggest the presence of this lesion. In his paper on "Pulmonary Arteriosclerosis," Ulrich<sup>11</sup> expresses much the same thought when he says: "By the simple expedient of finding no, or very little, evidence of congestive failure at the base of the lungs, when clinically there is a large liver, evidence of ascites and edema, the diagnosis of primary pulmonary sclerosis can be established." It would be more conservative to say that the syndrome of failure or abnormal strain of the right side of the heart without other obvious cause indicates obstruction in the lesser circulation, the exact cause of which must be otherwise determined.

Barnes and Yater<sup>12</sup> report a case of a man, aged 34 years, who died from failure of the right ventricle due to ancient thrombus in the pulmonary arteries. This man had two severe attacks of pain in the chest with intense dyspnea, apparently signaling the arrival of emboli in the lungs. He also had cyanosis, polycythemia, peripheral

edema and bilateral hydrothorax. At the postmortem examination, fairly well-organized thrombi were found in the pulmonary arteries between the main trunk and the subdivisions into their smaller branches. The right ventricle was much hypertrophied and the pulmonary artery much dilated.

A patient of Jump and Baumann,<sup>13</sup> with pulmonary thrombosis showed marked cyanosis, dyspnea, moderate edema and died shortly with signs of failure of the right heart. He lived long enough, however, to develop a fairly high-grade secondary polycythemia of 7,700,000 and marked right ventricular hypertrophy. The valves were all normal. Both main branches of the pulmonary artery were nearly filled with adherent thrombotic material. Jump and Baumann say: "Mechanically, the thrombus resembles the obstruction seen in congenital stenosis of the pulmonary artery. This obstruction puts additional weight on the right side of the heart, and hypertrophy follows. The cyanosis occurs because of slowing of the blood flow, and anoxemia comes from a greater utilization of oxygen by the tissues."

Since the only communication between the bronchial artery and the pulmonary arterial system is by way of the pulmonary capillaries, and not by way of vascular connections of respectable size, it is very unlikely that a collateral circulation in the lungs can be developed through the bronchial artery to compensate for obstruction in the main branches of the pulmonary artery, at least so far as respiratory function is concerned. Moreover, since the bronchial artery carries arterial blood, it is a little difficult, anyhow, to see what assistance in the business of oxygenation a circulation through it could furnish. In the absence of an adequate collateral circulation a reduction in the capillary bed must necessarily be accompanied by a reduction in effective respiratory surface area. We feel, therefore, that whether obstruction be in the main branches of the pulmonary artery or in the arterioles, anoxemia is due in great measure to inadequate re-oxygenation in the lungs.

**III. Sclerotic and Inflammatory Lesions of the Small Arteries and Arterioles.** Usually two forms of pulmonary arteriosclerosis are described: (1) Primary, and (2) secondary. The primary form is rare, of obscure etiology, and affects chiefly the small arteries, arterioles and capillaries. The larger vessels may or may not be involved. It has been called arteriolocapillary fibrosis of the lung and compared to the similar condition in the kidney. Moschcowitz,<sup>14</sup> who relates all pulmonary arteriosclerosis to increased pulmonary arterial pressure and doubts the existence of a primary form, says: "The resemblance between lesions of the pulmonary capillaries in hypertension of the lesser circulation and those of the glomerular capillaries in essential hypertension is striking, and in almost every respect they are identical." It produces a narrowing, even obliteration

tion of the small vessels of the lung, which results on the one hand in serious interference with respiratory function and on the other in adding to the burden of the right heart by increasing pulmonary arterial pressure. In this paper our interest is not so much in the etiology of the condition as in its effects upon respiratory function.

The secondary form is more common, involves the larger arteries and is apparently ascribable to the increase in pulmonary arterial pressure from down-stream changes in the heart and lungs (mitral stenosis, emphysema, pulmonary fibrosis). It may be associated with a generalized arteriosclerosis. As Pund and Phinzy<sup>15</sup> put it, these changes are usually without clinical significance or are overshadowed by symptoms produced by the primary disorder.

Moschowitz says that the difference between arteriosclerosis of the pulmonary circulation and that of the major system is solely one of intensity of the process. He thinks alveolar capillary lesions are pathognomonic of hypertension of the lesser circulation and its consequent arteriosclerosis, and that the thickening and hyalinization of the alveolar capillary wall embarrasses gas exchange and produces anoxemia. Increase of pericapillary connective tissue, which may reach the proportions of a true interstitial infiltration, is the result of a progressive interference with the blood supply.

Three cases (1 of Frothingham,<sup>16</sup> 1 of MacCallum<sup>17</sup> and 1 of our own) are now summarized to illustrate the effects of obstruction in the smaller pulmonary vessels upon oxygenation and the right ventricle. Frothingham reported a case of extensive bilateral progressive thrombosis of the smaller branches of the pulmonary arteries in a woman, aged 38 years, whose chief complaint was increasing shortness of breath. Severe pains under the left breast and a tendency to syncope were symptoms that remind us of similar attacks in the cyanotic group of congenital cardiac defects and were probably due to the same cause, namely, anoxemia. Cyanosis on slight exertion was marked, the red cell count was slightly increased, the electrocardiogram indicated right ventricular preponderance, the Wassermann reaction was negative and the vital capacity was 53 per cent of normal. She became gradually more cyanotic and short of breath even at rest, and finally died struggling for breath. "One of the attending physicians remarked that had the symptoms developed suddenly it would be the typical picture of an embolus in the pulmonary artery." At the postmortem examination, Frothingham found an extensive thrombosis which began in the smallest branches of the pulmonary artery and propagated centripetally toward the larger branches. Practically all pulmonary arterial branches of the third and fourth orders were completely occluded by thrombi which varied in size from pinhead-sized masses firmly attached to the vessel wall to similar appearing masses, 1 or 2 cm. in length, and filling the whole lumen of the vessel. The

alveolar walls showed considerable increase of connective tissue about bloodvessels and bronchi. In some regions the alveolar walls were almost avascular. Frothingham notes that the lesions in this case were different from ordinary arteriosclerosis, also from syphilis and from other cases of thrombosis of the pulmonary artery and suggests that it may possibly represent a unique lesion of the pulmonary arteries. He states that it resembles more closely thromboangiitis obliterans than any other condition.

MacCallum<sup>17</sup> has reported a case of "obliterative arteriolosclerosis" of the lung. He says that this obscure condition has been found only once in 12,000 autopsies at the Johns Hopkins Hospital, and that only 40 to 45 similar cases have been reported in detail. The essential clinical and pathologic features of his case are as follows: A colored woman, aged 39 years, complained of great breathlessness and pain about the heart upon exertion. If the exertion was continued, loss of consciousness followed. Physical examination showed moderate dyspnea and cyanosis. The superficial veins of the neck were engorged and pulsating. Fine moist râles were heard at the bases of both lungs behind. The heart was enlarged both to the right and to the left, the pulmonic second sound was accentuated and the closure of these valves easily palpable. The liver was enlarged and there was slight polycythemia. The electrocardiogram showed right ventricular preponderance. At the postmortem examination the heart was found to be much enlarged, the right auricle enormously distended. The right ventricular wall was 8 mm. thick and the left 12 mm. The mitral and aortic valves and coronaries were normal. The pulmonary artery was thickened and much dilated. The liver visibly collapsed when the venæ cavæ were cut. The most important finding was a widespread obliterative arteriolosclerosis.

A somewhat similar case came under our observation. A man, aged 38 years, entered the Colorado General Hospital complaining of shortness of breath, pain in the stomach and asthma of many years' duration. Physical examination showed moderate dyspnea and cyanosis, many râles, asthmatic in type, throughout both lungs, a slightly enlarged heart with faint diastolic and doubtful pré-systolic murmurs, edematous lower extremities. The Wassermann reaction was negative; hemoglobin, 115 per cent; red blood cells, 6,950,000 to 7,250,000. The electrocardiogram indicated right ventricular preponderance. He went steadily downhill and died with signs of failure of the right side of the heart.

At the postmortem examination, the right auricle was greatly dilated, the right ventricle was dilated and hypertrophied, its wall measured 8 mm. in thickness. The pulmonary orifice was slightly dilated. The aorta, the pulmonary artery and its large branches, the pulmonary veins, coronary arteries and heart valves were all

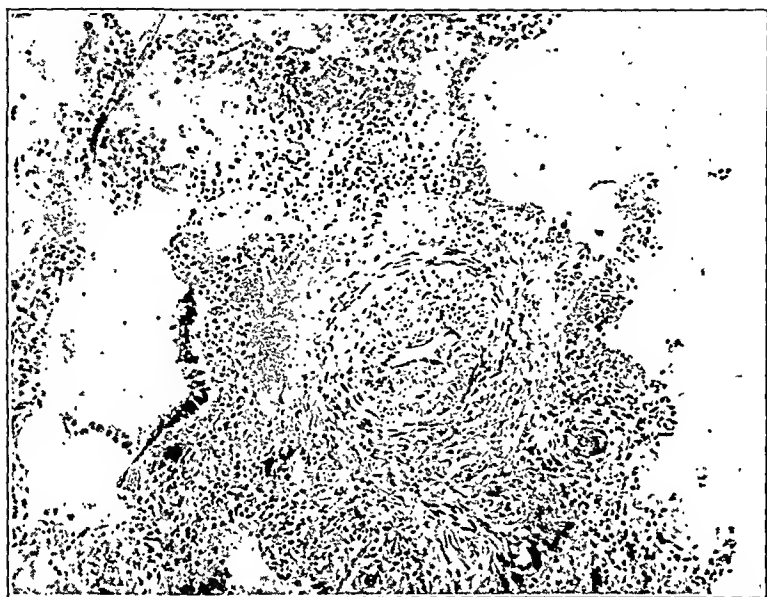


FIG. 2.—Vascular lesion showing thickening of the vessel wall with narrowing of the lumen. ( $\times 50$ .)



FIG. 3.—Small pulmonary artery showing thickening of the intima and infiltration with leukocytes. ( $\times 100$ .)



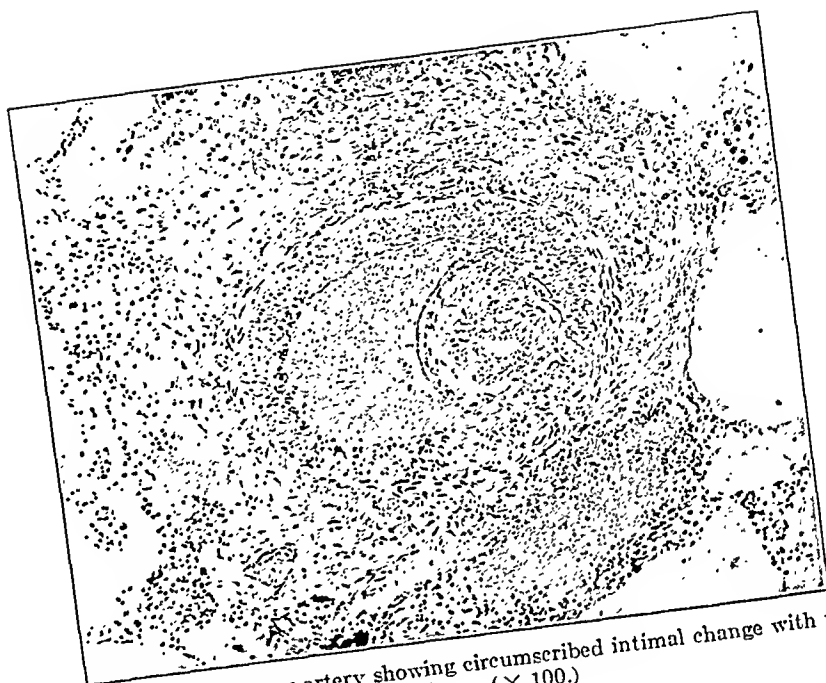


FIG. 4.—Small pulmonary artery showing circumscribed intimal change with partial obstruction. ( $\times 100$ .)

normal. Almost all of the smaller pulmonary arterics and pulmonary arterioles showed varying degrees of an inflammatory process causing partial or complete occlusion of these vessels. Practically all vessels intermediate in size between the arterioles and arteries, 1 to 2 mm. in size, showed some degree of intimal thickening and many contained hyalin thrombi. Histologically the lesion was not a typical arteriosclerotic process but essentially an inflammatory fibrous intimal thickening with partial or complete occlusion of arteries and arterioles and with thrombosis of larger, otherwise normal, arteries. Neither fat nor lipoid was demonstrated in the lesions (Figs. 2, 3 and 4).

Although the etiology of these differing vascular lesions is obscure, these 3 cases (MacCallum's, Frothingham's and our own) demonstrate that obstruction in the smaller arteries and arterioles eventually produces chronic anoxemia and right ventricular hypertrophy.

**IV. Processes Which Affect Primarily the Capillary Bed.** Thus far we have considered those forms of obstruction in the lesser circulation in which the location of the obstruction is more or less distant from the capillary bed. In these instances the capillary bed is affected indirectly, since the pulmonary arterial current is blocked higher up. The capillary bed may also be reduced by diffuse lesions which involve it primarily. These lesions, if they are sufficiently extensive and slowly progressive, may likewise by their mechanical obstructive action produce right ventricular hypertrophy and by direct obliterating effect upon the capillaries interfere with oxygenation. The clinical expression of all this will be again the syndrome of cyanosis, dyspnea and right ventricular hypertrophy, with the addition of polycythemia, provided constitutionally depressing influences, such as those which are usually associated with infectious processes, do not interfere with blood formation. Representative of these conditions are extensive pulmonary fibroses and the pathologic processes found in severe long-continued chronic bronchitis, asthma and emphysema. Yegge and one of us (J. J. W.<sup>18</sup>) recently reported a case of this latter type in which the effects of obstruction in the capillary bed were greatly exaggerated by hard work and the low oxygen tension of high altitude. This patient, a lumberjack, long a sufferer from bronchial asthma, who had worked for many years at 10,000 feet altitude, showed the clinical complex of intense cyanosis, dyspnea, polycythemia (maximum red cell count, 8,350,000), somnolence and right ventricular hypertrophy. At the postmortem examination the right ventricular wall measured 14 mm. and the heart valves were normal, the pulmonary artery and all its branches were greatly dilated. The lungs showed marked emphysema, much pulmonary fibrosis, and the typical picture associated with bronchial asthma, namely, thickening and hyalinization of the basement membrane of the bronchi, hypertrophy of the smooth

muscle in the bronchial walls, infiltration of the bronchial walls with lymphocytes and eosinophils. The bone marrow showed moderate hyperplasia. The clinical diagnosis in this case was failure of acclimatization because of hard work at a high altitude, secondary polycythemia, cardiac decompensation, emphysema and bronchial asthma, terminal bronchopneumonia.

**Summary.** 1. Primarily obstructive lesions of the pulmonary circulation which involve extensively the pulmonary capillaries or pulmonary arteries and are not immediately fatal: (a) Raise the pulmonary arterial pressure and produce hypertrophy of the right ventricle, and (b) interfere with respiratory function and produce anoxemia.

2. The clinical evidence of chronic anoxemia are commonly dyspnea, cyanosis and polycythemia, rarely precordial pain and syncope.

3. Signs of slowly developing strain upon the right side of the heart in the absence of other obvious cause, such as valvular defects, suggest obstruction in the lesser circulation.

4. Whether the obstruction be in the capillaries, as in certain instances of so-called Ayerza's disease, or in the arterioles and small arteries, as in MacCallum's case; Frothingham's case, and our case here reported, or whether the obstruction be in the larger divisions of the pulmonary arteries, as in the case of Means and Mallory, the underlying clinical picture of chronic anoxemia and failure of the right side of the heart is essentially the same.

5. This survey of the symptoms of obstruction in the lesser circulation has been undertaken to emphasize the too frequently forgotten importance of the integrity of the pulmonary circulation in the process of oxygenation.

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**COR BIATRIATUM TRILOCULARE WITH RUDIMENTARY RIGHT VENTRICLE, HYPOPLASIA OF TRANSPOSED AORTA, AND PATENT DUCTUS ARTERIOSUS, TERMINATING BY RUPTURE OF DILATED PULMONARY ARTERY.**

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COR BIATRIATUM TRILOCULARE is a heart with two auricles and one ventricle. A variation of this type of cardiac anomaly is one which has a rudimentary ventricle as well as a common large ventricle. Although anatomically this is a 4-chambered heart, for practical purposes it functions mostly as a 3-chambered organ. One or the other of the great vessels (usually the aorta) arises from the rudimentary ventricle. Because of the rarity of this type of anomaly, and also because of the unusual termination by rupture of the pulmonary artery, the following case is reported.

**Case Report. Past History.** Andrew T., was born in Hungary on September 21, 1913. His father is living and well; his mother died in 1916 of heart disease, age unknown. One older sister, who has supplied most of the information concerning the early history of the patient, is in good health. Two brothers died shortly after birth, cause unknown.

From birth the patient was a typical "blue baby." The cyanosis persisted throughout life, being aggravated by exertion and cold weather. Although he could perform the usual duties incident to childhood, his activities were curtailed by dyspnea and palpitation on moderate exertion. According to his sister, he was a bright boy in school, and always made good marks. He graduated from junior high school at 17. This may seem contradictory, but it may be said that his life was beset with domestic difficulties, which were not conducive to studious application. In the evenings he would sell papers and work in a toy shop. After graduation from school he sought work in various cities. It was during this period that he collapsed in the streets of Philadelphia, and was rushed immediately to the hospital on April 10, 1932. For 1 week prior to his collapse he had a non-productive cough.

**Physical Examination.** On admission to the hospital the patient was suffering with intense precordial pain and dyspnea. The pulse rate was 110; the respirations, 24; the temperature, 97.3° (axillary). Examination revealed a well-developed, well-nourished youth, apparently in agony. The entire body presented a dusky hue, and the lips and extremities were distinctly cyanotic. The fingers and toes showed pronounced clubbing. The pupils reacted normally. The buccal mucous membrane was deeply injected. The lungs showed impaired resonance and râles at the bases posteriorly. The area of cardiac dullness was increased to the right and left. The great vessel area also appeared to be increased. Auscultation revealed a systolic murmur in the pulmonic area, accompanied by a thrust. A diastolic murmur was heard in the aortic area. The systolic blood pressure was 80 mm., the diastolic, 60. The pulse was regular in rate, force, and rhythm.

*Laboratory Findings.* An electrocardiogram (Fig. 1) taken on the following morning was interpreted by Dr. G. D. Geckeler as follows: "Normal sinus rhythm with Q-R-S complexes in Leads II and III of exaggerated amplitude (often seen in cases of congenital heart disease and aortic insufficiency). All waves are deformed by induction house current. How much effect this has in changing the character of the P waves in Leads II and III, and of the T waves in the same leads, is questionable. P-R interval measures 0.18 second, and the Q-R-S interval measures 0.9 second. Unfortunately, the patient died before another tracing could be made."

A roentgenogram of the chest (Fig. 2) showed an enormous enlargement of the heart and great vessels. The peculiar outline of the cardiac shadow is accounted for by the unusual shape of the heart and the hemopericardium found at autopsy.

The hemoglobin was 100 per cent (standard = 16.92 gm. hemoglobin per 100 cc.). Unfortunately, a red blood count was not made. The white blood cells numbered 12,900; the polymorphonuclears, 71 per cent; lymphocytes, 27 per cent; transitionals, 2 per cent. The blood Wassermann and Kahn tests were negative. The chemical examination of the blood revealed the following findings: glucose, 125 mg.; urea nitrogen, 23 mg.; creatinin, 2 mg., per 100 cc. of blood. The urine showed a faint trace of albumin, pus cells, and several hyalin and granular casts.

*Course.* The patient lived for 28 hours from the time of admission. The pain and dyspnea continued unabated. The axillary temperature varied from 99° to 100°. The pulse reached its highest rate of 120 a few hours before death. The respirations fluctuated between 24 and 40. One-half hour before death the patient was still complaining of severe precordial pain. At the time of his death his age was 18 years, 6 months and 20 days.

*Autopsy Findings.* (Autopsy performed approximately 20 hours after death.) The body is that of a fairly well-nourished, well-developed, young male adult, about 20 years of age. There is cyanosis of the lips and fingers. The fingers and toes present drum-stick enlargement of their distal third. This clubbing is rather extreme, and the fingers are affected to a greater degree than the toes. The panniculus adiposus is well preserved.

Exploration of the thoracic cavity reveals the following:  
*Heart.* The cardiac area is enlarged in all directions, but lies chiefly on the left side. The pericardium is distended and has a reddish-blue color. On opening the pericardium, its cavity is filled with approximately 800 cc. of bloody fluid and blood clots. Around the base of the great vessels, the clots are quite adherent to the underlying structures. Careful removal of these clots reveals a markedly dilated, and ruptured pulmonary artery the source of hemorrhage. The visceral pericardium covering this vessel has two longitudinal tears on the anterior surface, and another similar tear on its posterior surface. It is separated from the structures beneath by clotted blood. The wall of the pulmonary artery contains multiple ruptures, which will be described in more detail later. Other features noted at this time are aortic hypoplasia and patent ductus arteriosus. The heart is hypertrophied and has a globular shape, with a blunted apex. No ventricular division can be discerned by external examination (Figs. 3, 4).  
 A closer study of the specimen several days later, after preservation in Kaiserling solution, reveals the following additional findings: The heart, including part of the descending aorta and main pulmonary branches as shown by the photographs and diagram, weighs 700 gm. When immersed in water it displaces 950 cc. of fluid.

*Auricles.* Both auricles are hypertrophied. The right auricle presents no anomalies, while the left has two pulmonary veins emptying into the cavity instead of the usual four. The interauricular septum has an anatomi-

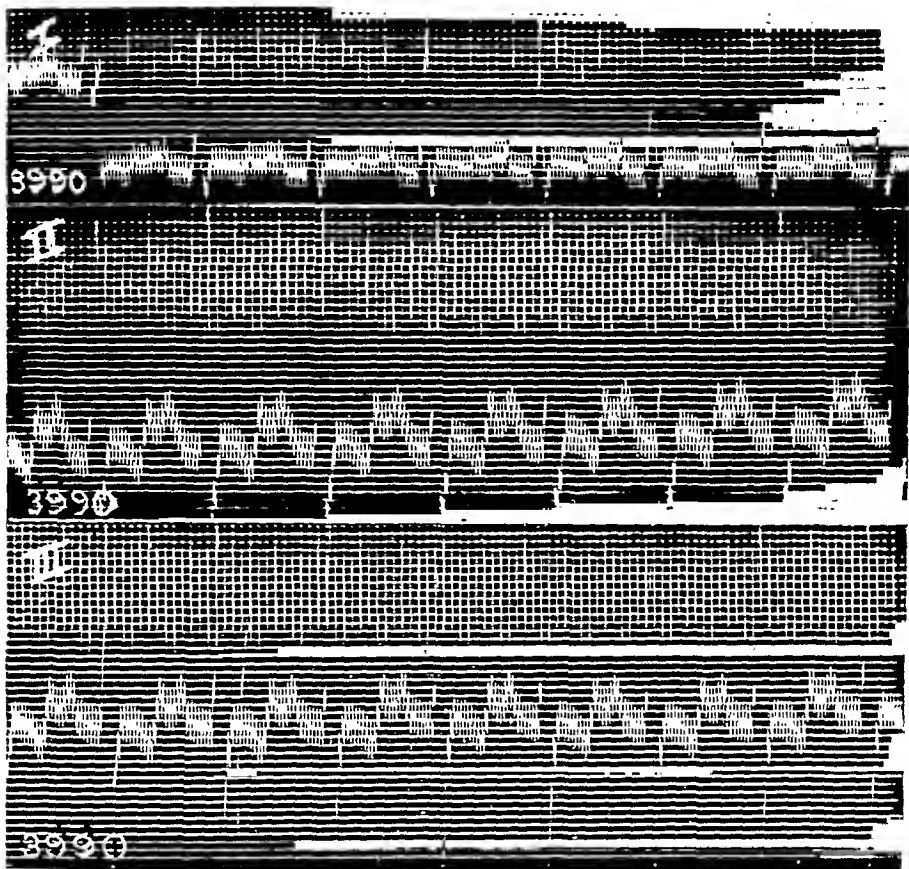


FIG. 1.—An electrocardiogram made on the day of the patient's death, showing exaggerated amplitude of the *Q-R-S* complex in Leads II and III.



FIG. 2.—A roentgenogram of the patient made on the day of his death. Note the enormous enlargement of the cardiac and great vessels shadow.

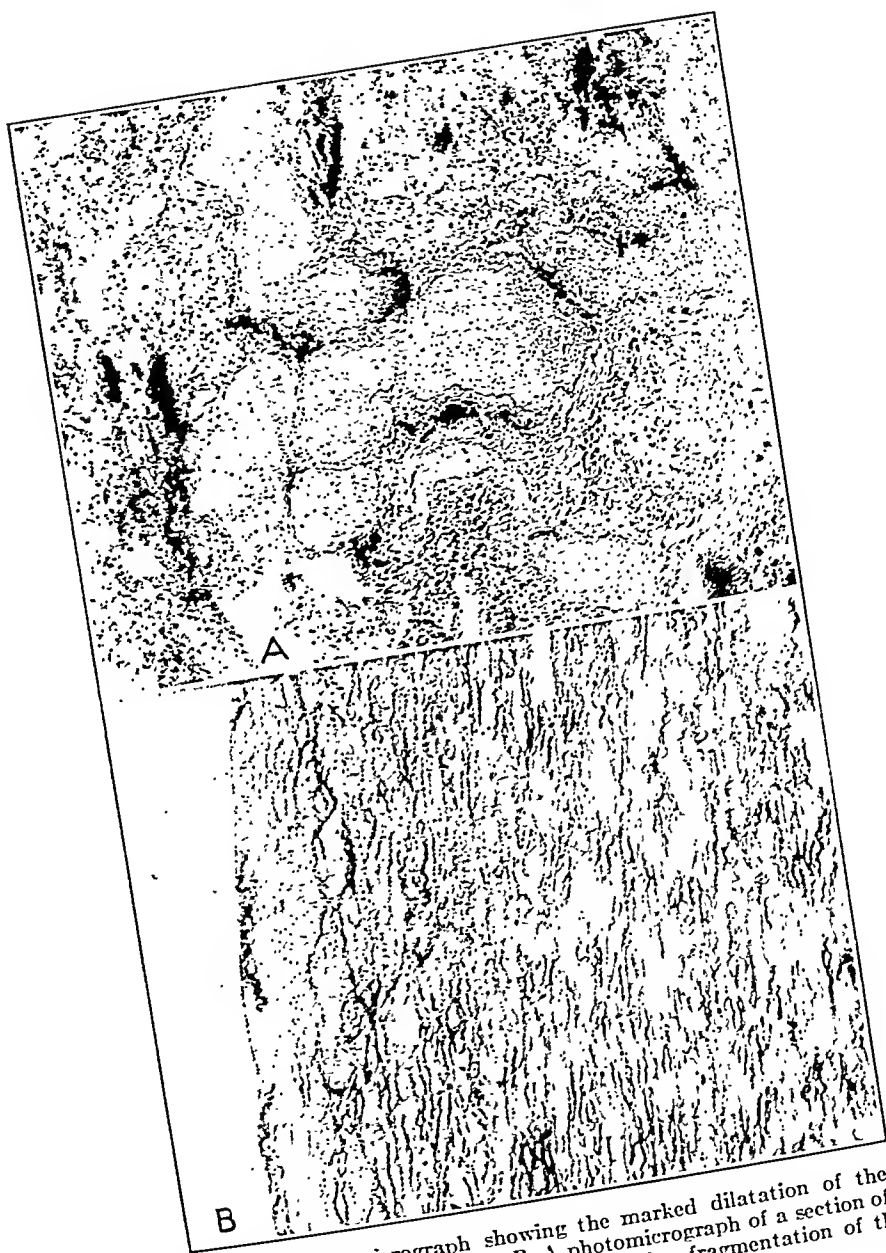


FIG. 6.—A, A photomicrograph showing the marked dilatation of the smaller vessels of the pulmonary circulation. B, A photomicrograph of a section of the pulmonary artery stained with Weigert's stain, showing fragmentation of the elastic fibers.

cally patent foramen ovale with overlapping edges. On the left side of the septum, one of the edges is supported by a short band which appears to be a continuation of the valve. Functionally, it is doubtful that admixture of auricular blood existed during life.

*Ventricles.* For all practical purposes one large ventricle exists, and contains the tricuspid, mitral and pulmonary orifices. On the extreme upper right quadrant is found a small ventricle containing the aortic orifice.

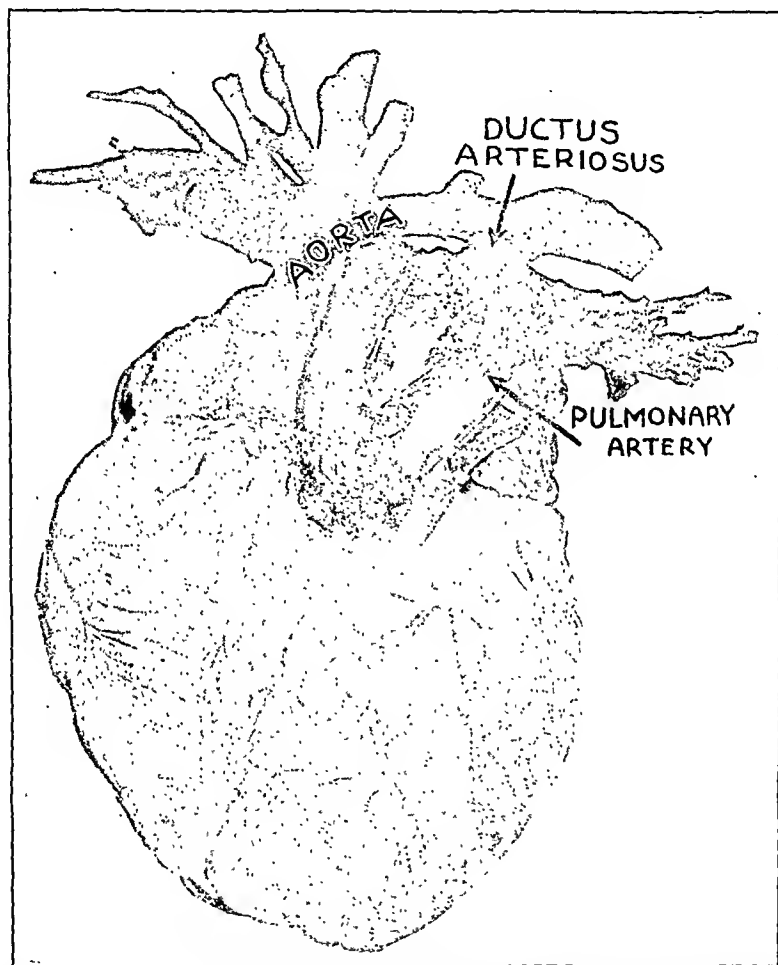


FIG. 3.—A photograph of the specimen, showing the globular shape of the heart, the dilated and ruptured pulmonary artery, transposition and hypoplasia of the aorta, and the patent ductus arteriosus.

The ventricles communicate by an interventricular septal defect at the base. The large ventricle has inside measurements of approximately 9 by 4 by 10 cm. The ventricular wall measures 2.1 cm. with trabeculæ, and gradually tapers to 0.6 cm. at the apex. The small ventricle measures approximately 3 by 3 by 6 cm. Its wall measures 1.2 cm. at the middle, and 0.4 cm. at the apex.

*Septum.* The interventricular septum is well developed below. Its upper third is absent and is replaced by an opening approximately 2 cm.



in diameter. A fenestrated appearance is imparted to this septal defect by the traversation of chordæ tendineæ of the tricuspid valve.

*Valves and Orifices.* The tricuspid orifice connects the right auricle with the large ventricle and is adjacent to the septal defect. The tricuspid ring measures approximately 4 cm. in diameter. The valve has a right and left leaflet of about equal size, and a smaller one posteriorly. The chordæ tendineæ of the right leaflet are partly attached to the interventricular septum, below the edge of the defect. When the valve is open, the right leaflet with its chordæ tendineæ partly closes the defect. The mitral ring measures approximately 3 cm. in diameter. The valve consists of a right and left leaflet. The chordæ tendineæ of the right leaflet are attached to

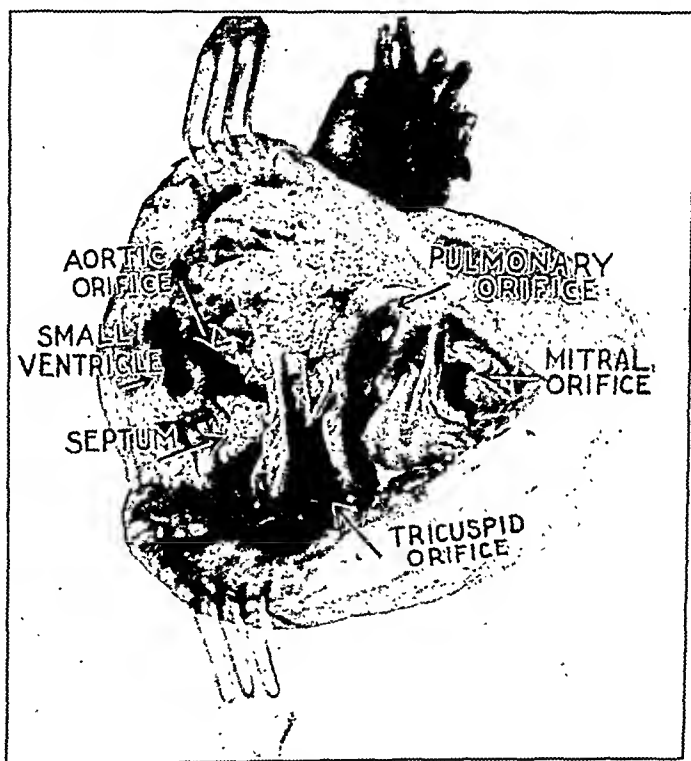


FIG. 4.—A photograph of the base of the heart viewed from below, showing the common ventricle, the defective septum, rudimentary ventricle, and the various orifices.

columnæ carneæ on the anterior and posterior ventricular walls. The pulmonary orifice arises from the large ventricle, between the tricuspid and mitral orifices, and anteriorly to them. Its diameter measures 2.5 cm. at the base of the semilunar valves. The valves show no anomalies.

*Pulmonary Artery.* The pulmonary artery shows a marked dilatation and multiple ruptures. The outside diameter slightly above the base measures 4.3 cm., while at the point of greatest enlargement, above the ruptures, it measures 5.6 cm. laterally, and 3.6 cm. anteroposteriorly. The ruptured portion of the artery is enveloped in blood clots. The visceral pericardial layer is separated from the structures beneath, and presents two irregular vertical tears anteriorly, and one posteriorly. The artery has a shattered appearance with complete separation of the wall. On the

anterior surface, 2.3 cm. from the base, there is a transverse linear tear involving about one-half of the anterior circumference. Another linear tear extends downward to the level of the semilunar valves. On the posterior surface, a diagonal irregular tear starts at the level of the transverse tear, and runs upward and to the right, to the level of the bifurcation of this vessel.

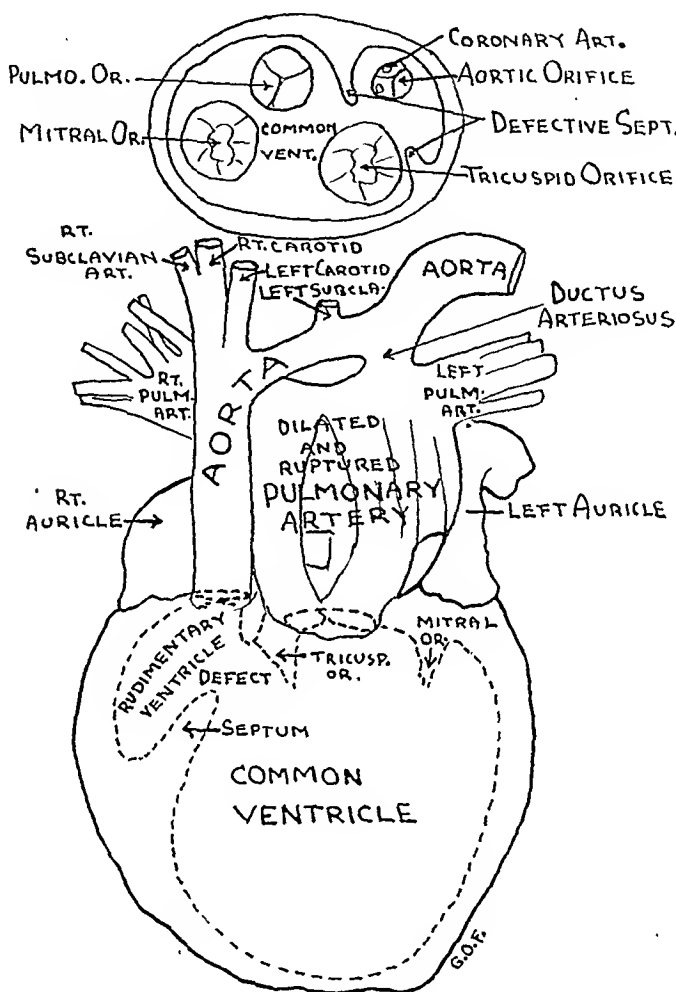


FIG. 5.—The upper diagram is a schematic representation of the base of the heart viewed from above. It shows the relative position of the various orifices. The aorta is transposed to the right into the rudimentary ventricle, and lies in the same plane as the pulmonary artery. The tricuspid, mitral, and pulmonary orifices are located in the common left ventricle. The lower diagram shows the other features of the heart and vessels.

The branches of the pulmonary artery appear short and dilated. The left branch measures 1.5 cm. in length and 2.5 cm. in diameter. It breaks up abruptly into numerous small radicles. The right branch is 2.5 cm. long and 2.5 cm. in diameter. It gives off 4 small branches. After continuing for a distance of 1.2 cm. it also breaks up abruptly into numerous small radicles.

*Aorta.* The aortic orifice is located at the base of the small ventricle, 1.2 cm. from the septal defect. It measures 0.9 cm. inside diameter, at the

base of the semilunar valves. The aorta is hypoplastic and is transposed to the right. The vessel gradually diminishes in size and reaches its smallest outside diameter at the arch, between the left common carotid artery and the left subclavian artery. Here it measures 0.7 cm. in diameter. Incidentally, these vessels are widely separated, the left common carotid arising near the base of the innominate artery. Beyond the ductus arteriosus, the aorta measures 1.8 cm. in external diameter. The aortic semilunar valves are 3 in number, 1 anteriorly, and 2 laterally. The coronary arteries arise behind the anterior and the left semilunar cusps.

*Ductus Arteriosus.* The ductus arteriosus is well developed and has a rather wide lumen. It measures 0.3 cm. in length and 0.8 cm. in diameter. The remainder of the autopsy findings are relatively unimportant. The lungs are dark red in color and congested. On section, a frothy, serousanguinous fluid exudes. The gastro-intestinal tract is negative. The liver is slightly larger than normal. On section, it presents a congested appearance. The gall bladder, pancreas, adrenals, and spleen are grossly normal. The kidneys are normal in size and shape. The capsule strips off easily, revealing a dark red, smooth surface. On section, there is general congestion. The urinary bladder, prostate, and ureters are grossly normal.

*Microscopic Examination.* The lungs reveal a generalized edema. The smaller vessels are markedly dilated and distended with blood. The sections of the pulmonary artery taken near one of the ruptures show hemorrhagic infiltration of the adventitia and the adjacent media. The media is edematous and its fibers are widely separated. Sections stained with Weigert's stain show fragmentation and separation of the elastic fibers. The liver shows passive congestion limited to the central zone of the lobules. The kidneys have congested capillaries and cloudy swelling of the tubular epithelium (Fig. 6).

*Summary of Salient Features.* The auricles, through their respective auriculoventricular orifices, communicate with a large common ventricle. The foramen ovale is anatomically patent, but is probably closed functionally. The pulmonary artery is dilated, ruptured, and arises from the common ventricle. A septum, defective at the base, separates this ventricle from a rudimentary one situated in the upper right quadrant. A transposed and hypoplastic aorta arises from the base of the rudimentary ventricle. The ductus arteriosus is widely patent, while the pulmonary veins are two in number. The smaller vessels of the pulmonary circulation are dilated.

*Review of the Literature.* Since cardiac anomalies are numerous and concomitant, it is possible that this condition may have been described under other titles. Abbott<sup>1</sup> was able to collect 11 similar cases. A careful search of the literature failed to add to this number. The author has been able to study the original reports of 10 of the 11 cases. Not all of these cases were identical in their main anomalies. For the sake of comparison, we have used the following anatomic criteria: (1) a common large ventricle, receiving the auriculoventricular orifices and the orifice of one of the great vessels; (2) defective interventricular septum; (3) one of the great vessels leading into the rudimentary ventricle.

Seven cases conformed with the above requirements. Holmes<sup>2</sup> patient was a male, aged 22. This case is unique, because the pulmonary artery springs from the rudimentary ventricle. Peacock's<sup>3</sup> patient was a child aged 8 months, while Rokitansky's<sup>4</sup> was a male aged 30 years. In addition, Rokitansky's case presented anomalies

of the openings of the vena cava and the pulmonary veins. Marchand's<sup>5</sup> and one of Spitzer's<sup>7</sup> cases were practically identical with ours. Another case described by Spitzer<sup>6</sup> was that of a child aged 5 months, and lacked a tricuspid opening. Mill's<sup>8</sup> patient was a child, who, in addition to the major defects, also had 3 coronary arteries and coarctation of the aorta.

The other 4 cases included in this group by Abbott<sup>1</sup> are those of Rokitsansky (second case), Chiari, Theremin, and Mann. Chiari's report was not available to the author. A study of the other 3 cases shows that they resemble more closely the true cor biatriatum triloculare, since all ventricular orifices originate in the same ventricle. Theremin's<sup>9</sup> patient was an infant aged about 2 months. Rokitsansky<sup>10</sup> described the heart of a girl aged 10 years, in which the narrow aorta, a stenotic pulmonary artery, and the atrioventricular orifices communicated with a large right ventricle. The case reported by Mann,<sup>11</sup> and also by Young<sup>12</sup> was that of a male aged 35 years. The heart weighed  $1\frac{3}{4}$  pounds, and had a small fossa in the right upper quadrant continuous with the large common ventricle. Mann<sup>11</sup> cites similar cases by Kreyzig<sup>13</sup> and Duroziez.<sup>14</sup>

From the standpoint of rupture of the pulmonary artery the literature is quite meager. A careful survey revealed 8 cases. Dowse<sup>15</sup> described the case of a young woman without history of syphilis. The pulmonary artery presented an aneurysmal sac, about the size of a hen's egg, with a rent in the outer wall. The pulmonary valves were covered with vegetations. Duffield,<sup>16</sup> in reviewing the literature of dilatation of the pulmonary artery found 4 cases of rupture, including that of Dowse's. The other 3 cases with Duffield's references follow: Ambroise Paré (Observations on Aneurisms, by John E. Ericksen, London, 1844) described the case of a tailor, who, while playing ball died from rupture of the pulmonary artery. Adam's reference (second volume of *Trans. Calcutta Med. Soc.*) contained no comment, while Dlauhy's patient (*Viertelj. f. Prakt. Heilk.*, 1848) presented an aneurysm with rupture. No mention of congenital cardiac defects was made.

Arró<sup>17</sup> reported a case in 1882, entitled, "Rotura de la Arteria Pulmonar, Muerta Fulminante." The reference was obtained from the Index Medicus; original publication was not available, but the title is self-explanatory. Durno and Brown<sup>18</sup> described the case of a man, aged 33, who had a dilated and atheromatous pulmonary artery, with a small hole near its base. The pericardial cavity was filled with blood. Moench's<sup>19</sup> case was a woman aged 29 years with hemopericardium, widely patent ductus arteriosus, and aneurysmal dilatation and rupture of the artery. Vogt-Møller's<sup>20</sup> case report concerns a girl, aged 4 years with sepsis (streptococcic), congenital cardiac hypertrophy, localized minimal abscesses of the pulmonary artery and aorta followed by perforation of both vessels, and resulting in hemopericardium, heart tamponade, and death.

**Comment.** For the consideration of the pathogenesis of congenital heart disease the reader is referred to standard works on the subject, notably the monographs by Abbott<sup>1,21</sup> and Spitzer.<sup>22,23</sup> Of great importance are Spitzer's contributions, whose theory, as reviewed by Abbott,<sup>1</sup> is based on the phylogenetic relationship existing between the human and reptilian heart. A portion of the right ventricle representing the conus of the reptilian right aorta is closed in the normal human embryo by the clockwise torsion of the bulboventricular end of the primitive cardiac tube. Failure of the normal degree of torsion or "detorsion" results in the apparent shunting of the parts in counterclockwise direction, which not only brings the parts out of their normal position, but reopens the channel of the reptilian right aorta and obliterates the left ventricular aortic trunk normally present in the human heart. In lesser degrees of detorsion both trunks persist, fuse, and form an abnormally large aorta riding over the septum. Spitzer supports his contention with a graded series of 11 cases, dividing the various grades into 5 types. Two of his cases, which are similar to ours, he groups under Type IV, a "mixed" transposition whereby the pulmonary artery and the tricuspid valve are found in the mitral valve ventricle.

An analysis of the 7 cases that were similar to ours reveals the following points of interest. The age varied from 5 months to 30 years. The sex was mentioned twice, both being males. The status of the foramen ovale was cited in 5 cases, and it was found to be opened in 2 (Holmes,<sup>2</sup> Spitzer<sup>6</sup>); the ductus arteriosus was mentioned in 5 cases, and found patent in 3 (Spitzer,<sup>6,7</sup> Mills<sup>8</sup>). Other associated defects were anomalous openings of the vena cava and pulmonary veins (Rokitansky<sup>4</sup>), absence of the tricuspid orifice (Spitzer<sup>6</sup>), coarctation of the aorta, and supernumerary coronary arteries (Mills<sup>8</sup>).

Spontaneous rupture of the pulmonary artery from any cause is extremely rare. Moench,<sup>19</sup> in 1924, found 2 additional cases besides his own (reference of 1 was not given). The author was able to collect 8 cases from the literature. The available records failed to show the association of major cardiac anomalies with rupture of the pulmonary artery. In Moench's case, and in ours, the ductus arteriosus was widely patent. The rupture in the other cases was associated with small abscess of the arterial wall, aneurysmal dilatation of obscure etiology, and atheromatous changes.

Dilatations and aneurysms of the pulmonary artery are rather common. Henschen,<sup>24</sup> in 1906, collected 42 cases. Among recent reports may be mentioned those of Corsy,<sup>25</sup> Coleschi,<sup>26</sup> and Crouzon and Grenaudier.<sup>27</sup> Moench<sup>19</sup> believes that a patent ductus arteriosus is a most important factor in the etiology of dilatation, and incidentally, rupture, since many cases present such a defect. Certainly, this must have been true in our case. No doubt, the major portion

of the systemic blood flowed through the pulmonary artery and the ductus arteriosus, as the ascending and transverse aorta was hypoplastic. The added strain placed on the pulmonary artery eventually caused its dilatation and rupture. Other explanations, however, must be sought in those cases where there is a persistent patent ductus arteriosus without other congenital defects.

**Summary.** A young man, aged 18 years, was taken ill suddenly, suffering with an agonizing pain of 28 hours' duration, and presenting symptoms of congenital heart disease. The autopsy revealed hemopericardium and a large heart, with dilatation and rupture of the pulmonary artery, hypoplasia and transposition of the aorta, and a widely patent ductus arteriosus. The heart presented a variant of cor biatriatum triloculare, having a rudimentary right ventricle which gave origin to the aorta. The literature is reviewed from the standpoint of the cardiac anomaly and rupture of the pulmonary artery.

I wish to express my appreciation to Dr. M. E. Abbott for the helpful suggestions in the preparation of the article, and to Dr. L. W. Falkenburg for the translation of the German literature.

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## ENDOCARDITIS DUE TO A NEISSERIA PHARYNGIS ORGANISM.

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ENDOCARDITIS due to Gram-negative diplococci other than the gonococcus and the meningococcus is rare. In 1918 Schultz<sup>1</sup> first recorded an instance of acute vegetative endocarditis due to *Neisseria pharyngis sicca*. In 1932 Graef, de la Chapelle and Vance<sup>2</sup> described a similar case. This report presents the clinical, pathologic and bacteriologic findings in another case of fatal endocarditis due to a similar organism.

**Case Report.** Patient, J. R. (Unit No. 49813), Italian female, aged 21.

**Past History.** The patient was first seen in July, 1931. On this occasion the history and findings led to a diagnosis of chronic pelvic inflammatory disease. It was also noted that during the past 1 or 2 years she had experienced dyspnea and palpitation on exertion. Her heart was found slightly enlarged to the left, the precordial thrust was prominent, but no murmurs or thrills were present. The patient was referred to the Gynecological Clinic for treatment, but did not return to the hospital until August, 1932, when she registered in the Obstetrical Clinic. At this time she was 4 months pregnant. In the interim her health had been fairly good.

**Present Illness.** On August 12, 1932, the patient was admitted to the Rochester Municipal Hospital. She complained of headache, and of pain in the abdomen, back, right shoulder and several finger joints. Her illness had begun suddenly 4 days previously with severe occipital headache. The initial headache was followed within 24 hr. by fever, repeated shaking chills, and generalized muscle and joint pains. The pain became especially severe throughout the back. The abdominal pain, which appeared soon after the first chill, was diffuse, quite constant, and cramp-like in nature. Since the onset, marked urinary frequency and urgency with suprapubic pain and burning had been present.

**Physical Examination.** The patient was obviously acutely and critically ill. The mouth temperature was 38.2° C. (100.4°F.), the pulse rate 112, the respiratory rate 24. Almost all of the joints were tender on pressure and painful on even slight movement, yet none showed any increased heat, redness or obvious swelling. Examination of the lungs revealed only scattered râles at both bases. The heart was enlarged, the rhythm regular. The blood pressure was 95 systolic, 40 diastolic. Classic signs of stenosis of the mitral valve were present. The abdomen was everywhere tender on pressure, and in the lower quadrants, especially on the right side, some rigidity was noted. The uterus extended 3 finger breadths above the symphysis. Rectal examination revealed moderate diffuse tenderness. The neurologic examination was negative; specifically the neck was not stiff.

The white blood cell count on admission was 26,000 per cmm. with 96% polymorphonuclear neutrophils. The urine contained no sugar or albumin. Numerous epithelial cells, scattered leukocytes, and occasional hyalin and granular casts were noted in the centrifuged specimen.

**Course in Hospital.** Immediately after admission, the patient was given salicylates both by mouth and intravenously but without any amelioration

of her joint pains. The abdominal pain was most intractable and suggested the possible presence of an acute surgical condition. Operative intervention, however, was judged to be inadvisable. Forty-eight hours after admission the blood culture was reported to be positive, a Gram-negative diplococcus having been recovered in pure culture.

On the 4th day after admission, the joint pains subsided considerably, but the intense abdominal pain persisted and the abdominal distention progressed despite vigorous treatment. On the 5th day drowsiness was first apparent and the next day stiffness of the neck was noted. Lumbar puncture was performed immediately. The spinal fluid, under a pressure of 300 mm. of water, had a ground-glass appearance and contained 450 cells per cmm. Of these 98% were polymorphonuclear leukocytes. A few intracellular and extracellular Gram-negative diplococci were found in the



FIG. 1.—Vegetations from mitral valve. Bacterial strain (method of Brown and Brenn).  $\times 100$ .

stained smears. Despite the fact that the preliminary sugar fermentations with the organism recovered from the blood stream indicated that this diplococcus was not a meningococcus, it was decided to administer anti-meningococcus serum. Within a period of 24 hr. the patient received 60 cc. of New York State Antimeningococcus Serum intravenously, and 80 cc. intrathecally. She continued to be intermittently drowsy and delirious, and died on August 22, 1932, 10 days after admission.

*Autopsy.* The autopsy was performed by Dr. William Allen, August 22, 1932, 3½ hr. after death. The body was that of a young, well-nourished woman. Several small petechiae were noted on the chest. The peritoneal cavity contained approximately 1000 cc. of clear, amber-colored fluid. Each pleural cavity contained about 1000 cc. of a similar fluid.

*Heart.* The heart weighed 300 gm. The muscle was grossly normal but microscopically showed numerous minute focal abscesses. The tricuspid,



pulmonic and aortic valves were normal. The mitral valve was moderately but distinctly thickened and deformed. On the margins of the valve and extending down over the chordæ tendineæ were numerous, various sized, grayish, cauliflower vegetations (Fig. 1). Microscopically these areas showed hyalinization of the valve leaflets and vegetations containing large clumps of bacteria. The coronary arteries were normal.

*Lungs.* The lungs were edematous, but otherwise nothing pertinent was found. *Spleen:* The spleen weighed 350 gm. and contained two small infarcts. In the sections numerous emboli with clumps of polymorphonuclear leukocytes and bacteria were seen in the walls and lumina of the veins. *Liver:* The liver weighed 2300 gm. The cut surface showed many minute yellowish-gray flecks which microscopically consisted of collections of polymorphonuclear leukocytes in areas where hyalin degeneration of the liver cells had occurred. *Pancreas:* The pancreas showed some increase in connective tissue and a few collections of polymorphonuclear leukocytes. *Kidneys:* The kidneys each weighed 200 gm. Several anemic infarcts surrounded by zones of hemorrhage and cellular infiltration were present in the cortex. Many glomeruli showed distinct inflammatory changes. *Gastro-intestinal tract:* The alimentary tract was normal except for a small infarction in the small bowel. *Brain and spinal cord:* The brain weighed 1300 gm. The smaller vessels on the cerebral and cerebellar surfaces were considerably injected. There were numerous small collections of leukocytes throughout the parenchyma and in the meninges. The spinal cord showed similar collections of cells. *Genital organs:* The uterus contained an unmacerated fetus. Sections of fetal heart, liver and lung showed no evidence of a septicemia. *Anatomical Diagnosis.* Infected infarcts of spleen and kidneys. Hyalin mitral endocarditis. Subacute vegetative mitral endocarditis. Chronic emboli in heart and lungs. Early acute meningitis. Glomerulitis, and acute focal interstitial nephritis. Focal necrosis of liver. Early fibrinous pleuritis and pericarditis.

**Bacteriologic Studies.** Cultures were taken at autopsy from the heart's blood; from the pleural, pericardial, peritoneal, spinal and amniotic fluids; and from practically all of the organs. Gram-negative diplococci were recovered from the heart's blood, from a mitral vegetation, and from a splenic infarct. Direct smears from the mitral vegetations showed large aggregates of Gram-negative diplococci. These organisms were of uniform size, biscuit-shaped, and arranged singly or in pairs. With Gram's stain, they were uniformly and constantly decolorized. After prolonged cultivation but a considerable variation in the size of individual organisms occurred, but the staining characteristics remained constant.

*Cultural Characteristics.* Growth in Douglas' tryptic digest broth during the first 24 hr. was characterized by a faint diffuse clouding. Within the next 24 hr. large granular aggregates had formed at the sides of the tube and had settled to the bottom as a heavy sediment. "String" formation developed as incubation was continued.

*Colony Type.* On ascitic fluid agar, after 24 hr., the colonies were quite small (0.2 to 0.4 mm. in diameter), convex and finely granular, with a finely scalloped edge. After 48 hr. colony size varied from 0.5 to 1 mm. and a small central depression appeared at the apex.

of the convexity. After 72 hr. colonies up to 1.5 mm. in diameter developed. On hemoglobin serum agar and on Bradford's medium (Douglas' agar, ascitic fluid, 20% glucose and defibrinated blood) the colonies were definitely larger and quite moist. On plain blood agar the colonies were always smaller, more opaque, and distinctly less friable.

After 5 weeks' cultivation on the above media with transfers made every 4 days, growth was usually profuse in from 18 to 24 hr. and the colonies on blood agar became as large and moist as those on Bradford's medium. After being cultivated in Douglas' broth for several transfers and then replated, the organism again grew in small, rather dry colonies which in turn again became large and moist after several transfers on enriched solid media.

*Fermentation Reactions.* For the study of fermentation reactions, ascitic fluid agar slants containing the respective carbohydrates and Andrade's indicator were used. Acid formation was observed in four sugars within 24 hr. (sucrose, glucose, levulose, maltose) and in dextrin within 36 hr. No reaction was noted in any of the other carbohydrates tested (mannite, dulcitol, galactose, inulin, lactose).

*Virulence for Laboratory Animals.* Graded doses of freshly grown organisms were injected intraperitoneally into mice without producing any ill effects. The largest dose given to each of 2 mice was the washings from one ascitic fluid agar slant after 24 hr. of incubation. The washings from two similar agar slants were given without effect to each of 3 guinea pigs. One rabbit, used for the production of an immune serum, did not have any unfavorable reaction to any of the injections.

*Serologic Reactions.* *Agglutination.* Agglutination reactions with this organism were not carried out since spontaneous clumping occurred in normal salt solution.

*Precipitation.* Immune serum was prepared by giving a large male rabbit over a 40-day period a series of 10 intravenous injections of whole organisms washed from 24-hr. ascitic fluid agar slants. The antigen for use in precipitation tests was prepared as follows: The 24-hr. growth on an ascitic fluid agar slant was washed with saline and inoculated into each of two flasks containing 100 cc. of Douglas' broth. After growth for 48 hr. the broth from one flask was centrifuged free of organisms and the cells added to the second flask. One-half cubic centimeter of pure phenol (0.5%) was added and the incubation resumed for 5 days. The broth was then centrifuged and the clear supernatant fluid used as the antigen in the precipitation reactions. This material in a dilution of 1 to 256 gave a clear-cut precipitin reaction with the homologous immune serum.

In addition to the strain of *Neisseria pharyngis* obtained from the patient described in this report, two other strains were available for comparison. One of these, sent from Dr. F. B. Mallory's laboratory in Boston by Dr. M. S. Shilling, also came from a fatal case of

endocarditis. The other strain was supplied by Dr. G. W. Rake of the Rockefeller Institute, and was isolated from the throat of a normal individual. Dr. Rake considered this organism characteristic of *Neisseria pharyngis sicca*, insofar as the descriptions of this organism in the literature permit the use of the term "characteristic." For the purpose of control, antigens were similarly prepared from typical stock strains of *Neisseria catarrhalis* and *Neisseria meningitidis*. Thus in the precipitation reactions, 5 antigens all prepared according to the technique described above, were used as follows:

1. Antigen J. R., organism recovered from patient, J. R., the subject of this report.
2. Antigen Shiling, furnished by Dr. M. S. Shiling.
3. Antigen Rake, furnished by Dr. G. W. Rake.
4. Antigen catarrhalis, stock culture of *N. catarrhalis*.
5. Antigen meningitidis, stock culture of *N. meningitidis* (a mixture of 3 strains).

Using these 5 antigens precipitation tests, carried out with 6 sera, yielded the following results:

1. *Serum from patient J. R.* This serum contained no precipitin for any of the antigens prepared.

2. *Serum from rabbit immunized with organism J. R.* A positive precipitation to a titer of 1 to 256 was obtained with the homologous antigen. No crossing with the other antigens was observed.

3. *Serum from Dr. Shiling's patient.* A positive precipitation to a titer of 1 to 256 was obtained with the homologous antigen. Crossing occurred at a titer of 1 to 16 with antigens J. R. and Rake, but not with the other antigens.

4. *Serum from rabbit immunized with Dr. Shiling's organism.* A positive precipitation to a titer of 1 to 64 was obtained with the homologous antigen. Crossing occurred at a titer of 1 to 16 with antigen catarrhalis and at a titer of 1 to 4 with antigens J. R. and Rake.

5. *Commercial antigenococcus serum* and (6.) *New York State antimeningococcus serum*: These sera contained no demonstrable precipitins for the antigens used.

**Discussion.** Considerable variations after only a moderate number of transfers on artificial media are known to occur among Gram-negative organisms found in the nasopharynx.<sup>3</sup> The organism from the patient, J. R., showed these variations in colony characteristics, growth rate, and in the size of the individual organisms. At some stage in this varied state, a close similarity to various "typical descriptions" of *Neisseria pharyngis sicca* and to other unclassified<sup>4</sup> nasopharyngeal Gram-negative diplococci was found.

The patient did not develop in the blood any demonstrable precipitin against the infecting organism. The immune rabbit serum prepared with the J. R. organism contained precipitin only for the

homologous antigen, and no cross-reactions with the other antigens were found. The serum of Dr. Shiling's patient, however, developed a titer of 1 to 256 with the homologous antigen and showed some crossing with both the J. R. and Rake antigens.

The organisms received from Drs. Shiling and Rake were studied as to growth characteristics and sugar fermentations, in addition to the precipitin reactions. The sugar reactions were similar and constant on subculture for all three organisms. Colony type and size on different media varied no more than the cycle of changes noted on repeatedly subculturing on various media the J. R. organism alone. At some stage in the various manipulations, especially after several transplants on enriched solid media, all three organisms looked quite similar.

While these minor variations in cultural characteristics and perhaps in the precipitin reactions may depend solely upon environmental factors, it is suggested that the observed organisms might better be considered as belonging to the *Neisseria pharyngis* group, rather than to a single *Neisseria pharyngis sicca* strain.

**Summary.** A case of fatal endocarditis due to a Gram-negative diplococcus of the *Neisseria pharyngis* group is reported. A bacteriologic and serologic study of the organism is presented.

The author wishes to thank Dr. G. P. Berry for his assistance in the preparation of this report. He wishes to acknowledge also the kindness of Dr. G. W. Rake and Dr. M. S. Shiling in furnishing strains of *Neisseria pharyngis* organisms for comparative study.

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## A NEW METHOD OF PRODUCING HEAT IN TISSUES: THE INDUCTOTHERM.

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A NEW high frequency generator, specially designed to generate heat within living tissues by electromagnetic induction, has been developed. This apparatus meets the requirements of the field of

medical diathermy. The clinical application of the Inductotherm, as this device is called, both for local treatment and the production of electropyrexia is extremely simple, requiring merely the placing of a few turns of insulated cable around or about the part to be treated. No metal electrodes are required, and burns such as those which may result from improperly applied surface electrodes are, of course, prevented.

The Inductotherm is a vacuum tube oscillator, generating an alternating current with a frequency of approximately 12,000,000 cycles per second. The current is conducted through a flexible, heavily insulated cable which is wound around or about the part to be treated. This cable may also be wound into a pancake type of coil to be placed over the tissues which it is desired to heat.

Within the coil, through which the current from the device flows, there is set up an alternating magnetic flux, having the same frequency as the current in the coil. If a conductive material is placed within the coil an electromotive force will be induced in it. As a result of this induced voltage, eddy currents of the same frequency as the exciting current will flow in the conductive material.

If living tissue is subjected to the magnetic field of the Inductotherm there will be no neuromuscular response to the eddy currents induced in the tissue, because the frequency of these currents is very high, 12,000,000 cycles per second, far above the frequencies which elicit muscular contraction.

The eddy currents induced in the more conductive materials will be the more intense, and therefore the generation of heat per unit time will be greater in these than in the less conductive materials. Obviously, if a body composed of materials of different electrical conductivities, such as tissue, for example, is placed within the coil, the intensity of the eddy currents, and consequently the heating, will be greatest in the materials of greatest conductivity. The following simple experiment will demonstrate the selective heating characteristics of high frequency currents applied in this way.

A glass vessel containing an emulsion of paraffin oil and a small amount of water rendered conductive by the addition of a small quantity of salt is placed within the coil of the Inductotherm. In a short time steam will rise from the mixture. The temperature of the mixture at this point will be considerably less than the boiling point of water, indicating that the more highly conductive globules of water have been heated more rapidly than the paraffin oil. The electrical conductivities of the water and the paraffin oil in the experiment just described may be considered roughly comparable to the electrical conductivities of vascular and adipose tissue respectively.

Experiments were conducted by two of us<sup>1</sup> to determine the relative heating of saline solutions of various concentrations by

high frequency currents. Curve 3, Fig. 1, represents the relative heating of these solutions by the Inductotherm. The heating of physiologic saline solution, which has a concentration of 0.85 gm. sodium chlorid per 100 gm. solution, was taken as 100% and the heating of solutions of other concentrations expressed as percentages of this degree of heating. The experimental curve deviates slightly from the theoretical straight line because of heat loss by radiation and because of the slight change in conductivity with change in temperature and in specific heat of the solution with change in concentration and temperature. For the purpose of comparison, heating curves for diathermy and a high frequency electric field are plotted in

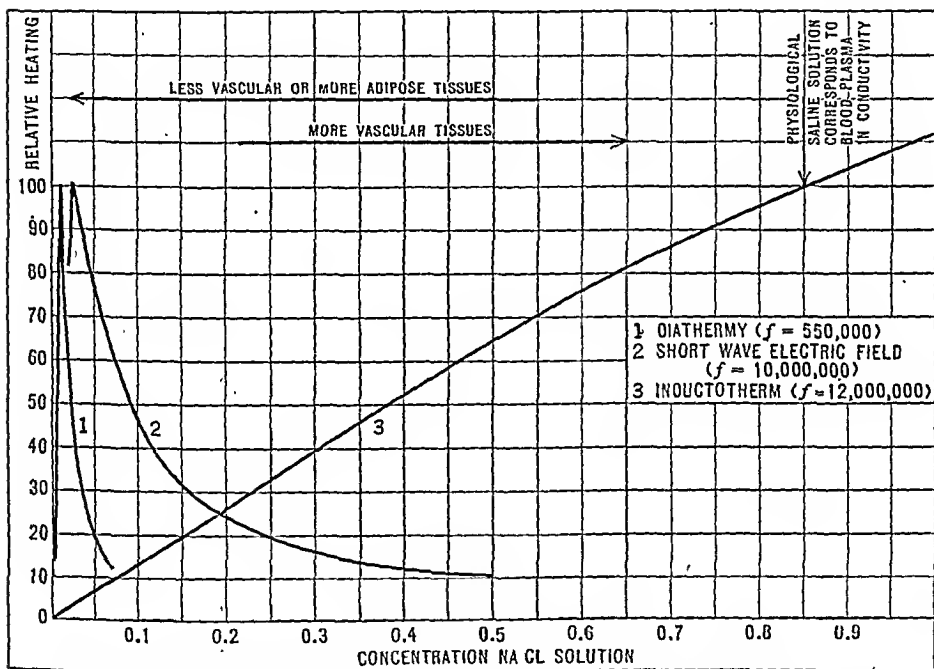


FIG. 1.—Heating characteristics of diathermy, high frequency electric fields, and the Inductotherm.

Fig. 1. Both diathermy and the alternating electric field produce maximal heating at a definite concentration. This maximal heating in each case was taken as 100% and the heating of solutions of other concentrations expressed as percentages of this degree of heating. It was observed that as the frequency of the current was increased, the point of maximal heating shifted to higher concentrations when the high frequency currents were applied by electrodes immersed in the electrolyte or by electrodes placed on opposite sides of the electrolyte with an air gap between each electrode and the electrolyte. Electrically, these two methods of application are essentially the same insofar as heating of the electrolyte is concerned, as was shown by Holmquest and Osborne.<sup>1</sup> It has been shown that for maximal heating

a definite relationship exists between the conductivity of the electrolyte, the dielectric constant of the electrolyte and the frequency of the current. To obtain maximal heating in an electrolyte having the conductivity of physiologic salt solution, by applying the high frequency current directly as in diathermy or by means of an electric field, it would obviously be necessary to employ a tremendously high frequency, so high in fact as to be impractical.

Physiologic saline solution has the electrical conductivity of blood plasma. As we decrease the concentration, we obtain saline solutions which correspond in electrical conductivity with less conductive materials such as blood, muscular tissue, etc., until finally we obtain a concentration electrically comparable to adipose tissue. From an inspection of the curves in Fig. 1 it is obvious that the Inductotherm alone, of the three means of heating tissue by high frequency currents, heats electrolytes in direct proportion to their electrical conductivities and hence will produce maximal heating in the most conductive tissues. The most conductive tissues are the most vascular tissues. In our opinion it is desirable to produce maximal heat in the vascular tissues rather than in the adipose tissues. The production of excessive heat in the underlying fatty tissues during the administration of high frequency currents by the usual methods is an important cause, in our opinion, of the discomfort experienced by many patients. The Inductotherm, which heats tissues in direct proportion to their conductivities, provides a means for the more comfortable treatment of patients having an unusually large amount of subcutaneous fat.

Through the courtesy of the General Electric X-ray Corporation, the Inductotherm has been used by us in animal experimentation and in the actual treatment of patients.

In all a total of 150 local treatments for arthritic joints were administered. The treatments comprised treatment of all the various joints of the body. In many cases several joints were treated simultaneously. The method of application was as described in a foregoing paragraph of this paper and illustrated in Fig. 2. The application was quickly and easily made and with no discomfort to the patient.

A total of 12 fever treatments were given by the Inductotherm. To produce fever the patient was placed in a treatment bag and two turns of the flexible cable placed around the patient and outside the bag (Fig. 3). Patients were selected so that all possible types might be represented. The weights of the patients treated ranged from 90 to 200 pounds. These patients had previously been subjected to other methods of producing fever, including hot baths, radiant heat and infra-red cabinets, electric blankets and diathermy.<sup>2</sup> The patients were more comfortable when the Inductotherm was used than when the other methods of raising temperature were employed. Figure 4 represents a typical 8-hr. graph of the rectal

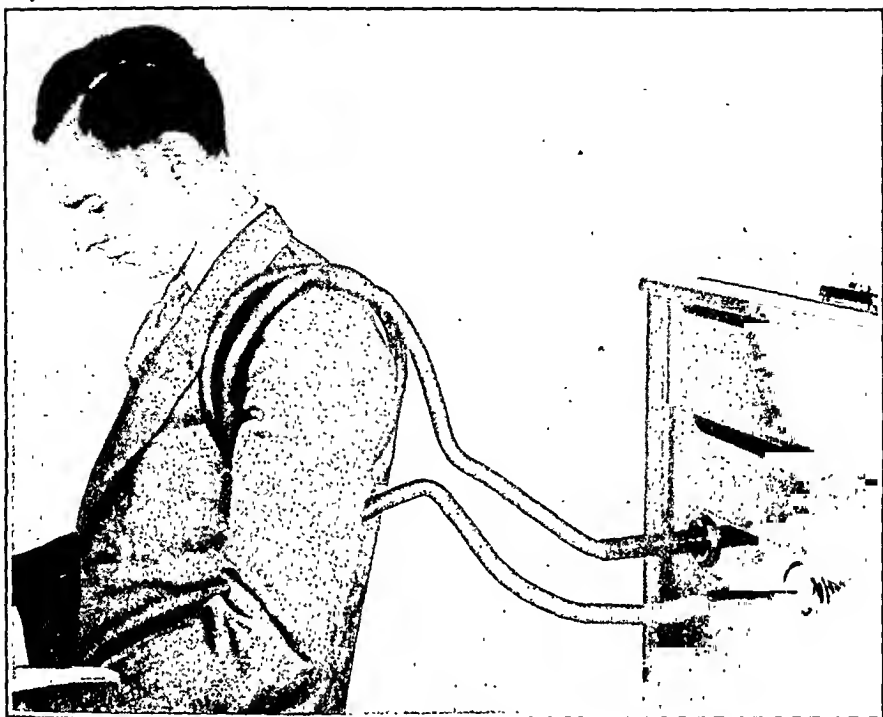


FIG. 2.—Treatment of shoulder by Inductotherm.

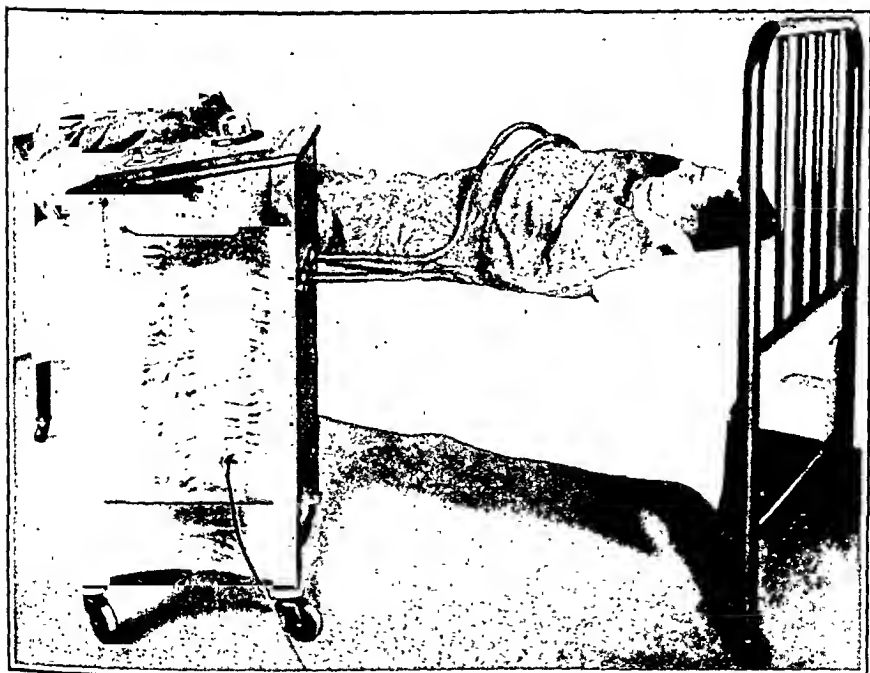
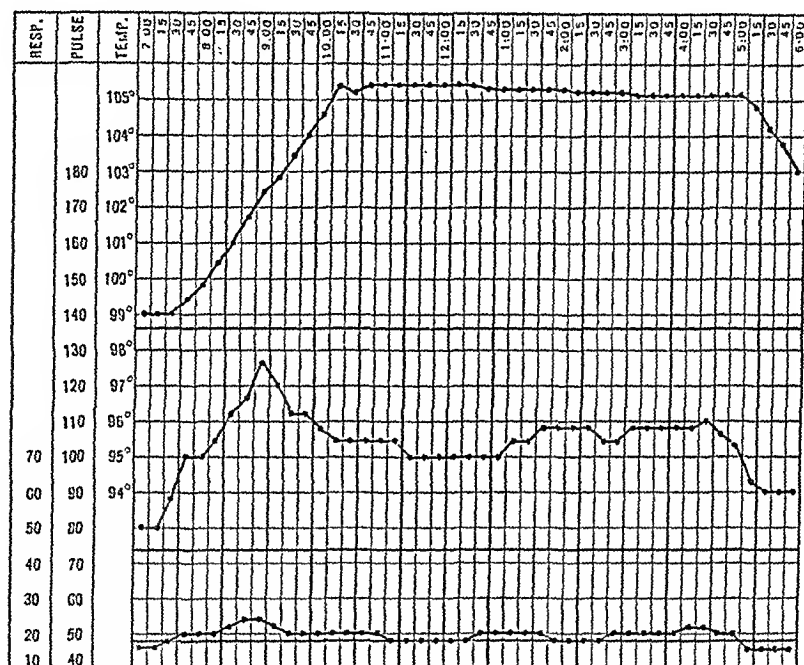


FIG. 3.—Electropyrexia by the Inductotherm.



temperature, pulse and respiration of a patient in whom electropyrrexia was produced by the Inductotherm.

The circulatory increase produced by the Inductotherm was observed to be great. This clinical observation is in agreement with actual measurements made by other research workers.<sup>3</sup> These investigators showed that the circulatory increase produced by the Inductotherm was as great as can be safely obtained by any physical means of producing artificial fever. From the data presented in their report one might draw the conclusion that no greater circulatory change can be obtained with safety by any method of producing artificial fever than was obtained with the Inductotherm. It is probably the maximal circulatory increase that it is physically possible to obtain.



and comfort of the patient, the Inductotherm in our opinion should become one of the most important clinical methods of applying heat to the tissues.

We wish to express our appreciation of the guidance and assistance of Dr. John S. Coulter, Director of the Department of Physicial Therapy, in whose department and under whose supervision this research was conducted.

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### ONE HUNDRED OBESITY DIETS ON ONE CHART.

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THE simplification of diet writing is an ever-pressing problem with the practising physician. Any attempt to be scientifically accurate in planning a diet for a patient is almost always attended with a degree of difficulty which requires more time and effort than most physicians can afford to give. The reason is that one who is not continuously writing diets finds it a problem to carry in his memory the carbohydrate, protein, fat and caloric values of common foods. If he carries with him a chart listing these values, he must then sit down and plan his diet on the basis of these figures. If he does not employ the method just described, then he must resort to the use of standardized diets found in most books on dietetics. Frequently he is unable to find a list of diets which is all inclusive and will meet the requirements of the individual patient under consideration.

The physician is therefore always looking for some simple method of diet writing which will obviate these difficulties and at the same time avoid tedious computations in his office practice. I described a simple chart (1) recently which was outlined to offer the practising physician a quick and ready means of arriving at a caloric diet for patients suffering from any disease necessitating the regulation of carbohydrate, protein and fat constituents. Although simple, it needs some degree of calculation and arrangement of a menu.

The present chart was devised to make available for direct reading and without any calculations whatsoever, 100 diets for cases of obesity. It is a small pocket-size folder containing two slides. The back of the chart contains the Index. One can read in the photograph the wide variety of obesity diet formulæ ranging from 600 to 1400 calories. In each caloric group there is a diversity of formulæ varying the carbohydrate, protein and fat contents. After

FACE OF OBESITY CHART.

DINNER		LUNCH		BREAKFAST	
31	Grams	31	Grams	31	Grams
80	Carb.	80	Carb.	80	Carb.
80	Prot.	80	Prot.	80	Prot.
18	Fat	18	Fat	18	Fat
800	Cal.	800	Cal.	800	Cal.
50	Grams 10% Fruit	50	Grams 10% Fruit	50	Grams 10% Fruit
2	Eggs	2	Eggs	2	Eggs
2	Unecda Discults	2	Unecda Discults	2	Unecda Discults
2	Grams Bread	2	Grams Bread	2	Grams Bread
cc. Milk	cc. Milk	cc. Milk	cc. Milk	cc. Milk	cc. Milk
30	Grams Meat, Fish or Fowl — Lean	30	Grams Meat, Fish or Fowl — Lean	30	Grams Meat, Fish or Fowl — Lean
30	Grams 5% Vegetables	30	Grams 5% Vegetables	30	Grams 5% Vegetables
75	Grams 10% Vegetables	75	Grams 10% Vegetables	75	Grams 10% Vegetables
75	Grams 20% Vegetables	75	Grams 20% Vegetables	75	Grams 20% Vegetables
75	Grams Cheese — Low Fat	75	Grams Cheese — Low Fat	75	Grams Cheese — Low Fat
75	Grams Cheese — High Fat	75	Grams Cheese — High Fat	75	Grams Cheese — High Fat
30	Unecda Discults	30	Unecda Discults	30	Unecda Discults
30	Grams Bread	30	Grams Bread	30	Grams Bread
30	Grams 10% Fruit	30	Grams 10% Fruit	30	Grams 10% Fruit
75	Grams 15% Fruit	75	Grams 15% Fruit	75	Grams 15% Fruit
cc. Cream	cc. Cream	cc. Cream	cc. Cream	cc. Cream	cc. Cream
cc. Milk	cc. Milk	cc. Milk	cc. Milk	cc. Milk	cc. Milk
250	cc. Buttermilk	250	cc. Buttermilk	250	cc. Buttermilk
120	Grams Meat, Fish or Fowl — Fat	120	Grams Meat, Fish or Fowl — Fat	120	Grams Meat, Fish or Fowl — Fat
100	Grams 5% Vegetables	100	Grams 5% Vegetables	100	Grams 5% Vegetables
100	Grams 10% Vegetables	100	Grams 10% Vegetables	100	Grams 10% Vegetables
100	Grams 15% Vegetables	100	Grams 15% Vegetables	100	Grams 15% Vegetables
100	Grams 20% Vegetables	100	Grams 20% Vegetables	100	Grams 20% Vegetables
75	Grams Cheese — Low Fat	75	Grams Cheese — Low Fat	75	Grams Cheese — Low Fat
75	Grams Cheese — High Fat	75	Grams Cheese — High Fat	75	Grams Cheese — High Fat
30	Unecda Discults	30	Unecda Discults	30	Unecda Discults
30	Grams Bread	30	Grams Bread	30	Grams Bread
75	Grams 10% Fruit	75	Grams 10% Fruit	75	Grams 10% Fruit
100	Grams 15% Fruit	100	Grams 15% Fruit	100	Grams 15% Fruit
cc. Cream	cc. Cream	cc. Cream	cc. Cream	cc. Cream	cc. Cream
cc. Milk	cc. Milk	cc. Milk	cc. Milk	cc. Milk	cc. Milk
250	cc. Buttermilk	250	cc. Buttermilk	250	cc. Buttermilk

Index 2

[illegible]

bread = 3 ounces  
= 20 grams high fat cheese

**OBESITY DIET** COLLINS, D.S.,  
 revised by WILLIAM S. Hospital  
 Israel-Zinn, N. Y.  
 Brooklyn, N. Y.  
 copyright 1933

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FIG. 2.—BACK FACE OF OBESITY CHART.

## INDEX TO OBESITY DIET FORMULAE

INDEX 1				INDEX 2				INDEX 3				INDEX 4			
Diet No.	Carb. grams	Prot. grams	Fat grams	Diet No.	Carb. grams	Prot. grams	Fat grams	Diet No.	Carb. grams	Prot. grams	Fat grams	Diet No.	Carb. grams	Prot. grams	Fat grams
600 CALORIES				800 CONT.				1000 CONT.				1200 CONT.			
1	30	30	40	26	110	60	13	51	125	50	33	76	100	80	53
2	50	30	30	27	60	70	31	52	150	50	22	77	120	80	44
3	40	40	30	28	80	70	22	53	60	60	58	78	60	100	62
4	50	50	22	29	100	70	13	54	75	60	51	79	80	100	53
700 CALORIES				30	60	80	27	55	90	60	44	80	100	100	44
5	40	40	42	31	80	80	18	56	110	60	36	81	120	100	36
6	50	40	38	900 CALORIES				57	125	60	29	82	80	120	44
7	60	40	38	32	70	40	50	58	150	60	17	83	100	120	36
8	40	50	38	33	90	40	42	59	50	70	58	1400 CALORIES			
9	50	50	33	34	50	60	50	61	90	70	40				
10	60	50	29	35	70	60	42	62	110	70	31	84	80	60	93
11	75	50	22	36	90	60	33	63	125	70	24	85	100	60	84
12	90	50	16	37	110	60	24	64	60	80	49	86	120	60	75
13	50	60	29	38	40	80	47	65	80	80	40	87	80	80	84
14	60	60	24	39	60	80	38	66	100	80	31	88	100	80	75
15	75	60	18	40	80	80	29	67	40	100	49	89	120	80	67
800 CALORIES				41	100	80	20	68	60	100	40	90	80	100	75
16	40	40	53	42	40	100	38	69	80	100	31	91	100	100	67
17	50	40	49	43	60	100	29	70	100	100	22	92	120	100	58
18	50	50	44	44	80	100	20	1200 CALORIES				93	150	100	45
19	70	50	35	1000 CALORIES								94	80	120	67
20	90	50	27	45	70	40	62					95	100	120	58
21	110	50	18	46	90	40	53	71	80	60	71	96	120	120	49
22	50	60	40	47	110	40	44	72	100	60	62	97	150	120	36
23	60	60	35	48	60	50	62	73	120	60	53	98	80	150	53
24	70	60	31	49	80	50	53	74	60	80	71	99	100	150	45
25	90	60	22	50	100	50	44	75	80	80	62	100	120	150	36

Directions:—Select in the table above the calories and formula you wish to give the patient. Then note the Diet Number to the left of the formula and the Index Number at the top of the column. Withdraw that Index card and reinsert so that the figures can be read through the window on the front face of the chart. When the Diet Number is seen in the window, read the menu for each meal. Substitution tables are found to the right of the window.

selecting the formula for the patient under consideration, the Diet Number to the left of the formula and the Index Number at the top of the column are noted. The Index is then withdrawn and reinserted so that the figures are visible through the window on the front face of the chart (Fig. 1). When the Diet Number appears in the window, the menu for the selected formula appears at the same time and can be read directly for each meal.

*For Example.* Suppose you wish to give a patient a diet containing 800 Calories. You can then select one of 16 diets listed for 800 Calories. If you choose a diet containing C 80, P 80, F 18, you will observe this to be Diet No. 31, Index No. 2. Withdraw Index No. 2 from the folder and reinsert so that Index No. 2 faces the window (see photograph of Front Face of chart).

The menu is then read directly as follows:

*Breakfast:* 50 grams 10% fruit

2 Uneda biscuits

30 cc. milk

*Lunch:* 75 grams cheese, low fat

30 grams bread

250 cc. buttermilk

*Dinner:* 120 grams meat, fish or fowl, lean

100 grams 5% vegetables

75 grams cheese, low fat

30 grams bread

250 cc. buttermilk

Coffee, tea, clear broth (fat-free) allowed with all meals.

A large list of substitution tables is presented on the Front Face of the chart which makes it possible to translate the weighed portions listed into approximate household measures.

The food values employed in preparing this menu chart are based upon average figures obtained from Bradley's Tables of Food Values.<sup>2</sup> The list of common foods from which these menus have been computed is as follows:

	Percentage carbohydrate.	Percentage protein.	Percentage fat.
Bread . . . . .	50	10	
Buttermilk . . . . .	5	3	0.5
Cereal, cooked . . . . .	15	3	
Cheese, low fat . . . . .	4	21	1
Cheese, high fat . . . . .	..	30	35
Cream, 20% . . . . .	4	3	20
Eggs (1) . . . . .	..	6	6
Fruit, 10% . . . . .	8	0.5	
Fruit, 15% . . . . .	15	1	
Meat, fish or fowl, lean . . . . .	..	20	10
Meat, fish or fowl, fat . . . . .	..	20	20
Milk . . . . .	5	3	4
Vegetables, 5% . . . . .	4	1	
Vegetables, 10% . . . . .	8	2	
Uneda biscuits (1) . . . . .	5	0.5	

**Summary.** A diet chart is presented which makes it possible to read the menu directly, without calculation, for almost any reduction diet a physician may wish to prescribe.

**NOTE.**—I wish to thank Miss Rose Kay for her assistance in preparing these diets.

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### SYMPTOMATIC RELIEF OF EMPHYSEMA BY AN ABDOMINAL BELT.\*

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IN obstructive emphysema, particularly in advanced cases, difficulty in breathing is due largely to mechanical factors. The voluminous lungs hold the diaphragm in the position of inspiration so that it can contract little, if at all. The chest is expanded to a barrel shape and further distention is limited no matter how great the respiratory effort. As these processes develop, there is a gradual reduction in the vital capacity of the lungs which at times reaches a point wherein the patient is totally disabled. The respiratory demands of even slight exertion cannot be met without distress.

The problem of facilitating breathing in emphysematous individuals by correcting mechanical defects, received considerable attention, especially in Germany, some 20 years ago. Various operative procedures and mechanical devices were advocated. Severance of costal cartilages in order to relieve intrathoracic pressure was recommended by Freund<sup>1</sup> and by Seidel.<sup>2</sup> Different types of apparatus were used, particularly pneumatic cabinets.<sup>3</sup> One was so regulated that compressed air encompassed the body during expiration so that a larger inspiratory excursion became possible. Another (the Waldenburg apparatus) could be regulated so that the patient inspired outer air but exhaled into rarified air, a procedure designed to reduce lung volume. The Bruns apparatus was of a similar nature but cheaper and more easily handled. The

\* Read in abstract form before the 48th Meeting of the Association of American Physicians, Washington, D. C., May 9, 1933.

Rossbach breathing chair and the Boghean breathing machine were mechanical instruments in which the patient was placed and the abdomen compressed during expiration. The Hofbauer apparatus carried out this process more simply. It consisted of a bag placed around the abdomen and attached to a tank of compressed air. A timing device permitted the bag to fill with air during each expiration. As a result abdominal compression was transmitted to the thorax and air was thus expelled from the lungs.

Breathing exercises and manual compression of the thorax for a period each day by a masseur were measures also recommended to overcome the mechanical handicaps to breathing in emphysematous individuals. Most of these procedures were either too cumbersome to be of use or not sufficiently effective to be generally adopted.

The observation that patients with advanced emphysema assume positions which compress the abdomen (leaning forward in the sitting posture, squatting on the haunches, tightening the belt) led to the development of the belt herein described. It was inferred that the increased intraabdominal pressure thus created was transmitted against the flattened diaphragm which would then be pushed upward toward its normal expiratory position. From that position excursion would again be possible. To confirm this supposition a patient was stood before the fluoroscope. An orthodiagram was made of the flattened diaphragm. As pressure was then exerted with the flat of the hand just above the symphysis pubis, the diaphragm rose and began to assume its normal dome shape. On deep inspiration the diaphragm descended and the patient stated that he was again getting air into his lungs (Fig. 1).

To maintain the diaphragm in its elevated position, a belt was devised. This is made of canvas and fits around the lower abdomen so that its lower edge rides just above the symphysis pubis. The upper edge comes well below the umbilicus. Just above the symphysis a leather or soft sponge rubber pad is fitted. This is suspended to the upper border of the belt by a band of spring steel, so bent that pressure is exerted inward and upward toward the promontory of the sacrum. The pad is 3 inches high, 5 inches wide and 1 inch thick. These measurements are approximate and vary with the size and habitus of the patient. The pressure of the pad against the abdomen varies according to posture. It is increased on sitting or bending forward, and lessened in the standing and reclining positions. These variations are obvious to the patient in that the belt feels too tight or too loose. To maintain a constant and comfortable pressure, a screw bolt in contact with the anterior face of the pad projects through the front of the belt. The patient can easily adjust the pressure by a turn or two of the screw head (Figs. 2, 3 and 4). The belt laces in the back and has thin round white rubber thigh straps. It is applicable to all but emaciated patients with sunken abdomens where there is little resistance to "press against."

Twenty-five patients with obstructive emphysema were fitted with abdominal belts. An orthodiagram and vital capacity determination before and after application were made in each case. With the exceptions noted in Table 1, these patients were kept under observations for periods varying between 2 and 6 months.

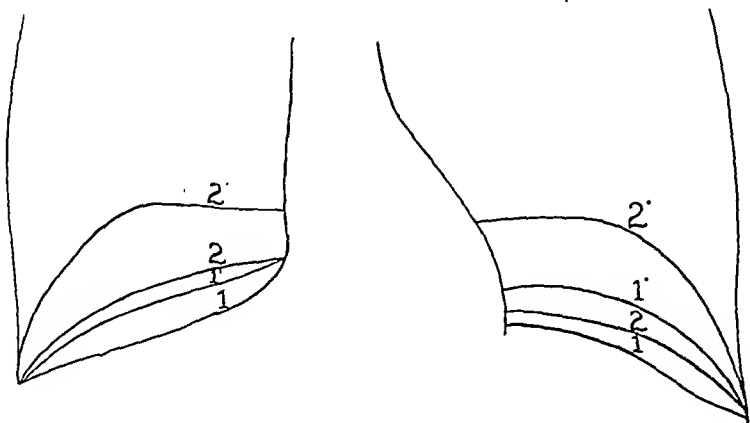


FIG. 1.—Orthodiagram of diaphragmatic positions in a patient with obstructive emphysema. 1', Expiration; 1, extreme inspiration; 2', expiration during abdominal pressure; 2, extreme inspiration during abdominal pressure.

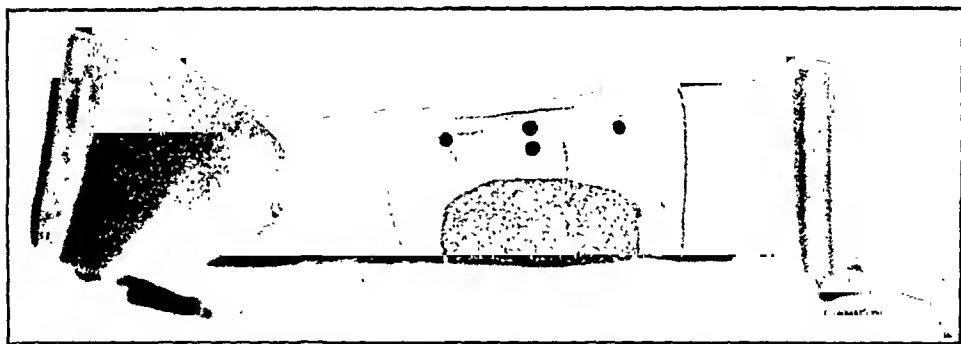


FIG. 2.—Inner face of belt, showing the pad. The 2 rivets vertically arranged are holding the spring steel to which the pad is attached.

Two patients whose vital capacities were increased could not or would not wear the belt. Four patients (1 with Ayerza's disease) after a fair trial maintained that the belt did not help them. The remaining 19 reported distinct subjective improvement. The average increase in vital capacity for the entire group was 39%. Of interest is the observation that the 1 patient who has worn the belt as long as 6 months has a restoration of excursion of his diaphragm even when the belt is not worn.

Intrapleural pressures were taken on a few patients before and after application of the belt. Similar pressure readings were made with the belt loosely in place and after it had been tightened. In



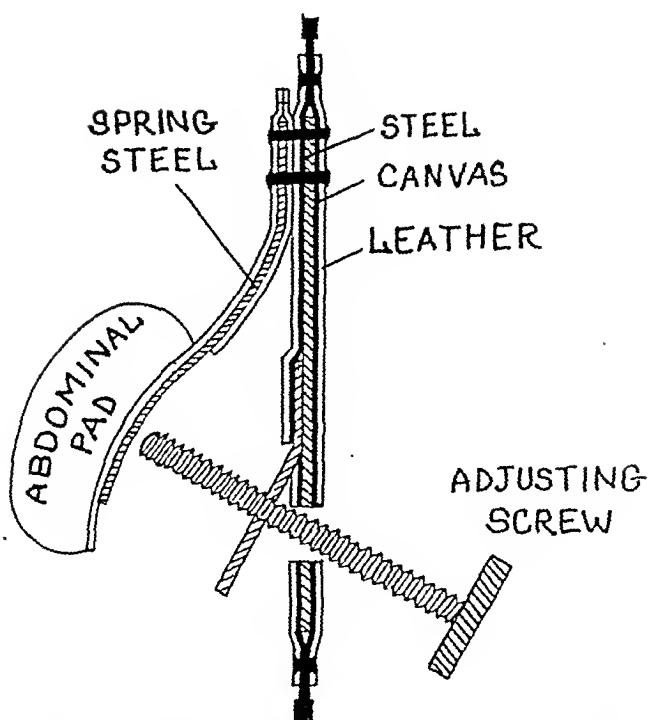


FIG. 3.—Schematic drawing of belt.

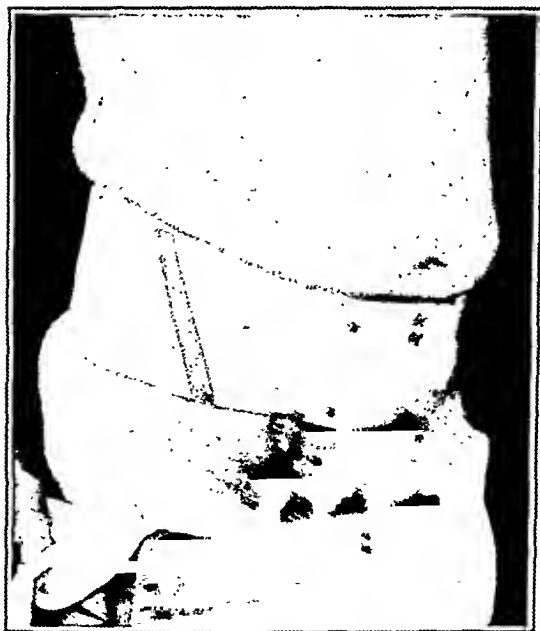


FIG. 4.—The belt in place. The screw head projects at the lower border in line with the 2 vertical rivets.

each instance the characteristically elevated intrapleural pressure of obstructive emphysema became *more negative* with the belt applied. For instance, expiratory and inspiratory values of +1 cm. of water and -3 cm. respectively, without the belt, became -2 cm. and -8 cm. with the belt in place. This effect is attributed to the fact that intrapleural pressure is influenced by the extent of respiratory excursion and thus falls as diaphragmatic movement becomes restored.

TABLE 1.—INCREASE IN VITAL CAPACITY AND SYMPTOMATIC IMPROVEMENT IN PATIENTS WITH EMPHYSEMA AFTER APPLICATION OF BELT.

Patient. No.	Etiology of emphysema.	Vital capacity.		Per cent increase.	Remarks.
		Before belt, cc.	With belt, cc.		
1 . . .	Bronchitis	1800	3200	77	Improved.
2 . . .	Bronchitis	2500	3300	32	Improved.
3 . . .	Asthma	1400	2200	57	Unable to wear belt.
4 . . .	Bronchitis	2200	3300	50	Improved.
5 . . .	Influenza	2500	3500	40	Improved.
6 . . .	Asthma	1700	2500	47	Would not wear belt.
7 . . .	Asthma	2500	3200	28	Improved.*
8 . . .	Bronchitis	3000	3700	23	Improved.*
9 . . .	Pulmonary sclerosis	1000	1400	40	No improvement.
10 . . .	Bronchitis	2900	3600	24	Improved.
11 . . .	Bronchitis	2400	3300	37	Improved.
12 . . .	Asthma	2250	3700	64	Improved.
13 . . .	Bronchitis	1500	2500	66	Improved.
14 . . .	Indeterminate	2250	2800	24	Improved.
15 . . .	Influenza	3500	4200	20	Improved.
16 . . .	Bronchitis	1100	1900	72	No improvement.
17 . . .	Bronchitis	2800	3600	28	Improved.
18 . . .	Bronchitis	2000	3100	55	Improved.
19 . . .	Asthma	2200	3100	40	Improved.
20 . . .	Bronchitis	1800	2600	44	Improved.
21 . . .	Bronchiectasis	2900	4000	37	Improved.
22 . . .	Bronchiectasis	2400	3400	41	Improved.
23 . . .	Bronchiectasis	2600	3200	23	Improved ?
24 . . .	Asthma	1100	1200	9	Improved.
25 . . .	Asthma	1600	1600	0	No improvement.

\* Did not return for further observation.

We observed no bad effects on the digestive system by wearing the belt. As a matter of fact, many of these patients with emphysema have a visceroptosis due perhaps to the pushing down of the viscera by the flattened diaphragm. Some of these patients said their abdomen felt better, but we have made no statistical observations on this point.

**Summary.** In advanced obstructive emphysema, difficulty in breathing is due principally to mechanical factors. The large lungs hold the diaphragm in the position of inspiration, and indirectly they also distend the chest to a barrel shape. Respiratory excursion is thereby limited.

It has been found that the diaphragm can be pushed upward toward its expiratory position by means of abdominal pressure, properly applied. From this position contraction again occurs.

In order to maintain adequate intraabdominal pressure, a belt has been devised. In a series of 25 patients with advanced obstructive emphysema to whom belts have been fitted, 19 have been subjectively improved. The average increase in the vital capacity of the lungs has been 39%.

With improvement in respiratory function, the characteristically elevated intrapleural pressure of obstructive emphysema has been found to become more negative and thus approach more normal values.

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### THE MECHANISM AND USE OF ABDOMINAL SUPPORTS AND THE TREATMENT OF PULMONARY DISEASES.\*

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In previous reports<sup>1,2</sup> it was shown that a decrease in pulmonary manifestations occurred in 2 tuberculous patients with enlargement of the abdomen. This improvement was attributed in part to the effects of diaphragm elevation favoring rest for the affected lungs. The first case was a pregnant woman with artificial pneumothorax on the left side. During gestation an elevation of the diaphragm occurred with an increase of pressure in the left pleural cavity, a shift of the heart to the right and a relative increase in "thoracic type" of breathing, indicating that the compression due to diaphragm elevation was considerable. After delivery the diaphragm excursions returned to lower levels, as in phrenicectomy cases following a regeneration of the phrenic nerve. This suggested that the sudden shift of the diaphragm, resulting in a preponderance of "abdominal type" of breathing, might explain certain instances of activity of tuberculosis following pregnancy. The second patient had enlargement of the liver and ascites. With the

\* Read before a meeting of the Section of General Medicine of the College of Physicians of Philadelphia, Philadelphia, November 27, 1933.

gradual increase in the abdomen there was a corresponding elevation of the diaphragm and decrease in fatigue, dyspnea, cough and expectoration. As observed in the first case the pulmonary features were such as would be expected in bilateral phrenicectomy.

It was pointed out in the discussion of these patients that diaphragm elevation could be obtained by using abdominal supports. This suggested a means for preventing the spread of tuberculosis following pregnancy. It was suggested further that the mechanism may be applicable for the treatment of chronic pulmonary diseases in which dyspnea and difficult expectoration were prominent features. To obtain further information on possible indications an evaluation of standard treatment was undertaken. This was intended especially to throw light on the rôle of mechanical factors in tuberculosis. Certain data and impressions have been incorporated in the present paper.

It is obvious that rest, nutritious diet and the patient's coöperative attitude are the most important influences in the treatment of pulmonary tuberculosis. Although physical characteristics may not be determining factors, it is perhaps true that thin individuals offer the least favorable prognosis. Artificial pneumothorax, phrenicectomy and thoracoplasty, used as supplementary measures in selected cases, have definite value due evidently to limitation of motion of the affected lung. The failures that occur following all types of treatment—even when the outlook has been encouraging—may be attributed to delays in discarding some measure or in adopting radical procedures. The indications for artificial pneumothorax are debated widely; some believe that it should be employed at the beginning even in early cases, others consider that its value has been overemphasized. This is equally true of thoracoplasty. Surgeons want cases that are not far advanced, while internists wish to delay operation until conservative measures have failed, admitting that later the prospects for satisfactory surgery are remote.

From such considerations it seemed as if some fundamental mechanism had perhaps been omitted. That this may account for certain failures in all forms of treatment seemed possible because of the occasional unexpected return or exaggeration of symptoms which apparently had been controlled. Deep and not well coördinated movements of the diaphragm as evidenced by heaving cough and feeble abdominal type of breathing were considered part of this uncontrolled mechanism.

Although the rest-dietetic régime is helpful in the management of pulmonary abscess and bronchiectasis, the results are not to be compared with its general value in pulmonary tuberculosis. This is due largely to the fact that suppurative conditions generally have disturbing systemic effects, as may be appreciated in comparing the clinical picture of tuberculosis with one of equal involvement of

bronchiectasis. In the latter there is in addition to loss of appetite, weight, strength, and elevated temperature the appearance of an extremely "toxic" state. Here perhaps the most successful of surgical measures is bronchoscopic drainage. Even when it fails as a cure, there is at least transient relief; but in order to obtain the greatest benefit bronchoscopy should be done 2 or 3 times weekly. In the majority of instances collapse measures are unsatisfactory, the least desirable results being obtained in artificial pneumothorax, the most favorable in phrenicectomy. The value of external drainage of lung abscess adjoining the chest wall is well recognized. In lobectomy, with new developments in technique, there may be a promising future for bronchiectasis. As a medical procedure so-called postural drainage may have definite value; success depends largely on the patient's coöperation and selection of the proper posture.

Various influences have been mentioned to explain the failures of collapse treatment in pulmonary abscess and bronchiectasis. Of these the marked sensitivity of the lungs to necrotic tissue products and interference with drainage due to compression of the bronchi have been noted. This occurs frequently in the use of artificial pneumothorax. A further disturbance may occur in phrenicectomy cases due to a loss in the expulsive force of the diaphragm.

The value of drugs in all forms of chronic pulmonary disease is debated widely; at best, the effects are symptomatic and often followed by disturbing manifestations. This is especially true in the use of opium derivatives in stopping cough, but with retention of secretion or with expectorants, where not infrequently gastrointestinal symptoms follow.

It seems fair to conclude, then, that the indications for using mechanical measures in pulmonary diseases are as important as the contraindications. This is emphasized in the favorable results that may be obtained from collapse therapy in pulmonary tuberculosis, and the harm that may result in suppuration. In order to obtain further data on the subject of mechanical influences measurements were obtained from collapse therapy in suppurative diseases during normal and forced respirations. The subjects were of different weight levels and had various respiratory diseases and stages. The excursions of the diaphragm and abdominal movements were obtained by means of silhouettes taken with the individual marked fluoroscopic screen and the chest and abdominal movements were studied by means of the diaphragm were studied with a camera in fixed positions. Differences in expansion and contraction of the chest and abdomen were calculated from a graph superimposed over the negatives when the photographs were developed. Measurements in Obese Patients. In both men and women there was usually a greater degree of thoracic than abdominal expansion. This was less striking in the pendulous abdomen than in the rotund

muscular form. Thoracic movements were relatively greater in the "athletic" type with broad shoulders and "well developed" chest. The diaphragm levels were usually lowest in the standing posture, especially in the patient with a relaxed pendulous abdomen. In all types the abdominal movements increased during sleep and relaxation. During cough the indrawing of the abdomen was limited almost entirely to the upper third and in some cases was scarcely perceptible.

**Measurements in Malnutrition.** In both men and women with progressive loss of weight there was usually a preponderance of the abdominal type of breathing, especially in the long, flat type of chest and scaphoid abdomen. During cough there was a marked general retraction of the abdominal wall followed by rapid expansion; the latter occurring with the sudden rebound of the diaphragm in deep inspiration. The excursions of the diaphragm during cough showed in several instances a higher level at the end of forceful expiration and a lower level during the next inspiration than would be expected in well-nourished individuals. These phenomena were exaggerated in advanced pulmonary diseases especially the preponderance of abdominal type of breathing. In patients with marked emphysema the "flattened" diaphragm, as reported previously by Alexander and Kountz,<sup>3</sup> was a feature.

Since there is usually a preponderance of "abdominal" breathing in pulmonary disease and relatively greater "thoracic" breathing in well-nourished and well-developed individuals it seemed of interest to study the effects of limiting lung motion in the verticle plane.

*Principle of Abdominal Support.* Accordingly a number of abdominal supports were devised and tried. Two principles were used: one to limit the expansion of the abdomen, the other to exert pressure from below upward on the abdomen and its contents. The problem was simplified in the subject with a large, well-developed type of abdomen. In this a suspensory model, consisting of a front piece made of heavy broadcloth cut somewhat diamond shaped and equipped with stays, buckles, straps and a back piece was entirely satisfactory. For individuals with less abdominal fat the stays in the front piece were bent and the concavity placed in apposition to the abdominal wall. In patients with large, relaxed pendulous abdomens, it was necessary to "tuck," as well as compress, the fat. For this purpose a support was constructed from an aluminum plate 8 cm. in width and 12 cm. in length. A pad of slightly smaller dimensions was attached to the under surface of the plate. The support is held in position by three sets of leather straps, buckles and a "form fitting" back. The proper adjustment is evident when rolls of fat rise above the borders of the plate and abdominal movements are not visible. In patients requiring considerable pressure over the abdomen, especially bed patients with dyspnea and ambulatory cases with bronchiectasis and considerable cough, a different design was found necessary. Fundamentally the same feature of compression was used but instead of "binder" construction, which causes approximately the same degree of pressure on all sides of the abdomen, the principle of central pressure was employed. The device consists of an aluminum plate somewhat the shape of a four-leaf clover, approximately 10 by 12 cm. in

diameter, enclosed in leather and cloth.\* Two tension springs 22 to 28 cm. in length covered with canvas which project at both ends in the form of straps pass over the aluminum plate at the upper and lower margins. These are curved slightly at the ends so as to follow the surface of the waist and hips. The straps are fastened to buckles attached to the back piece. Compression is obtained by bending the springs and tightening the straps (Fig. 1). A single spring fastened to the lower third of the support is sufficient for patients with moderate development of the abdomen.

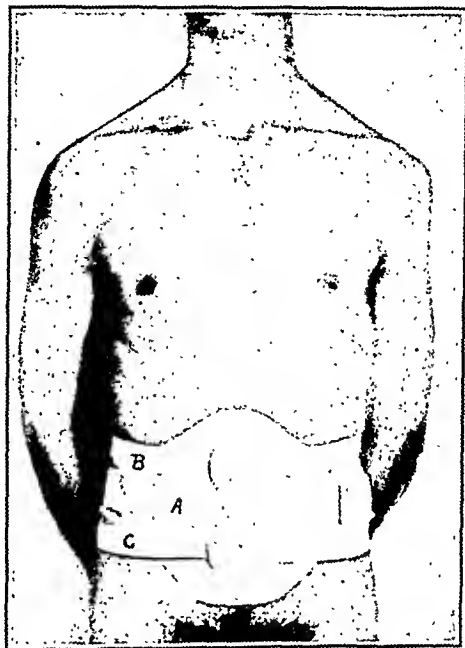


FIG. 1.—Type of abdominal support used for inducing considerable pressure over the abdomen. It consists of an aluminum plate "A" covered with cloth and leather and 2 steel springs terminating in tapes "B" and "C," which are adjusted to buckles on the back piece.

The abdominal supports were used in a group of 41 patients, with various pulmonary diseases, who had been on standard treatment for more than 6 months. Some patients had been observed for more than 4 years. The group includes: bronchiectasis, 6; so-called simple bronchitis, 2; chronic bronchitis and emphysema, 4; pneumoconiosis, 7; bronchial asthma with chronic bronchitis and emphysema, 4; pulmonary tuberculosis with considerable fibrosis, 18. There was no change in treatment except to increase exercise or discontinue unimportant procedures. In most instances the supports were worn day and night. All the patients were studied by Roentgen ray and anatomical measurements as in the preliminary studies and in a few instances vital capacity determinations were made. The occurrence of symptoms such as dyspnea, cough and the type and amount of expectoration were noted.

The immediate effects obtained from the use of abdominal sup-

\* These supports were developed with the assistance of Mr. J. J. Amsterdam, and Mr. R. K. Sennig, of Amsterdam Brothers, Inc., Philadelphia.



FIG. 2 A.—A drawing constructed on graph paper from the accompanying silhouette. The patient had moderately advanced tuberculosis and pneumoconiosis. The diaphragm level at full inspiration was calculated from the roentgenogram shown in Fig. 3 B, lines B. The elevation is designated as 53 mm. counted on the graph.

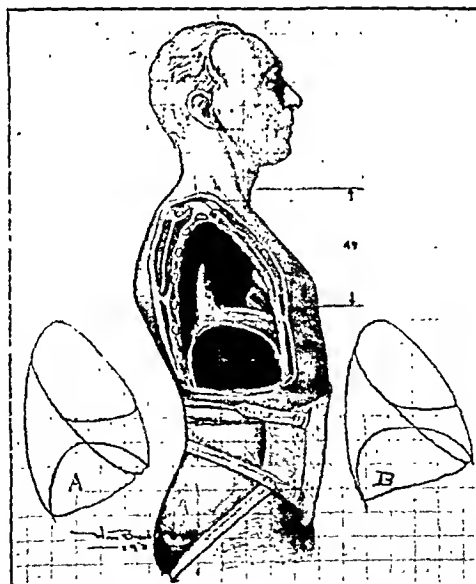


FIG. 2 B.—Drawing constructed from the silhouette of the same individual (2A), wearing a diamond-shaped abdominal support with steel stays. The diaphragm level at full inspiration was calculated from the roentgenogram shown in Fig. 3 A, the level being designated as 49 mm. counted on the graph. A comparison with 2 A will show a decrease in the transverse diameter of the abdomen and an increase in the diameter of the thorax. The changes in lung volume are illustrated in diagram B. In comparing this with diagram A (Fig. 2 B) the increase in the transverse dimensions of the lungs and the decrease in vertical dimensions are shown.



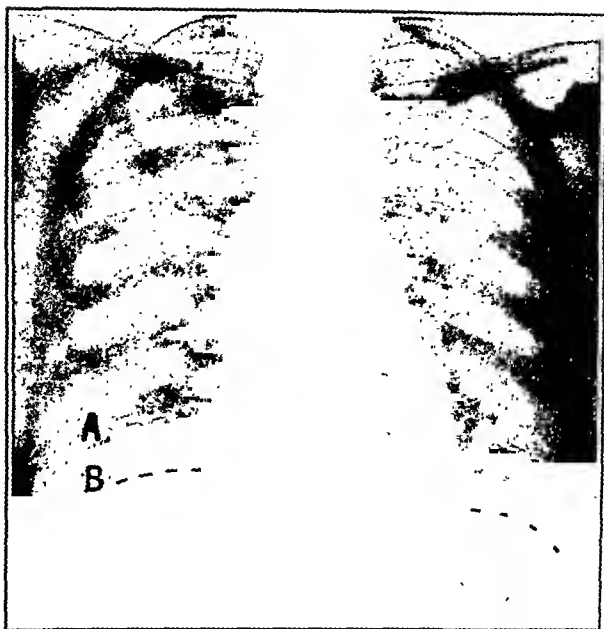


FIG. 3 A.—Roentgenogram of the same individual in full inspiration while wearing an abdominal support. The dotted lines "A" indicate the level of the diaphragm. Dotted lines "B" were obtained by superimposing Fig. 3 B over the roentgenogram and tracing the level of the diaphragm.

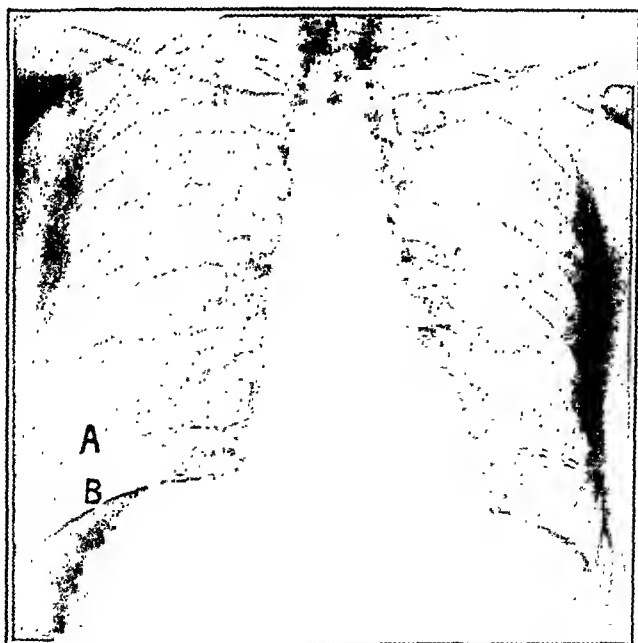


FIG. 3 B.—Roentgenogram of the same individual in full inspiration without an abdominal support. Dotted lines "A" show the level of the diaphragm which corresponds with "A" in Fig. 3 A. Dotted lines "B" show the level of the diaphragm without the use of an abdominal support and correspond with "B" in Fig. 3 A. The elevation was 2.5 cm.

TABLE 1.—THE EFFECTS (IMMEDIATE) OF ABDOMINAL SUPPORTS IN VARIOUS PULMONARY DISEASES.

Patient.	Diagnosis.	Symptoms without support.	Effects after wearing support.
H. O.	Pneumoconiosis	Marked dyspnea; cough and expectoration	Breathes easily; cough and expectoration decreased (expectoration marked at first); formerly in bed; now 1 hour exercise; support worn 3 weeks.
J. B.	Pneumoconiosis	Marked dyspnea; cough and expectoration	Dyspnea and cough decreased; expectoration increased first 2 weeks, then decreased; formerly on cure only; now 1 hour exercise; support worn 3 weeks.
H. C.	Pneumoconiosis	Practically invalid; cyanosis; marked dyspnea; cough and expectoration; pain in chest; and abdomen	Striking general improvement; cyanosis and dyspnea decreased; cough appears "higher" in chest and more productive; no pain; formerly in bed; now on cure and short exercise; support worn 4 weeks.
M. B.	Pul. tuberculosis (far adv.)	Dyspnea and cough; loss of weight	Dyspnea and cough decreased; gain in weight; formerly in bed; now on cure and 1 hour exercise; support worn 3 weeks.
J. L.	Pul. tuberculosis (far adv.)	Heavy breathing; cough and expectoration; weakness	Breathing "more with chest and easier;" cough less frequent; expectoration reduced, strength increased; formerly in bed; now on cure and $\frac{1}{2}$ hour exercise; support worn 3 weeks.
P. S.	Pul. tuberculosis (mod. adv.)	Cough and expectoration; "breathes heavily" on walking up a slight grade	Breathes easily at all times; cough and expectoration decreased; formerly on cure and 15 minutes exercise; now all-day cure and 1 hour exercise; support worn 4 weeks.
F. L.	Pul. tuberculosis (mod. adv.)	Cough and expectoration; "breathes heavily"	Breathes easily; cough less frequent; each cough more productive; formerly on cure; now on 1 hour exercise; support worn 4 weeks.
C. K.	Pul. tuberculosis	Dyspnea; weakness; loss of weight	Dyspnea decreased; increased strength and weight; in bed; support worn 7 weeks.
A. C.	Pul. tuberculosis (far adv.)	Dyspnea; cough and expectoration	Dyspnea less; increased thoracic movements; cough infrequent; each cough more productive; formerly in bed; now on cure and 1 hour exercise; support worn 5 weeks.
J. C.	Pul. tuberculosis; pneumoconiosis	Marked dyspnea; weakness; difficult expectoration; severe cough	Striking effects within 3 hours after support was applied; comfortable on lying flat in bed; formerly 4 pillows were necessary; expectoration facilitated and racking cough stopped; general appearance strikingly improved.
G. H.	Bronchiectasis (dur., 3 years)	Dyspnea and cough; foul expectoration and weakness; loss of weight	No dyspnea on walking; cough and expectoration decreased; sputum not foul; marked increase in strength; gain in weight; support worn 2 weeks.
G. V.	Bronchiectasis (dur., 9 years)	Dyspnea and cough; profuse expectoration; weakness; pain in abdomen	Dyspnea less; no pain; cough less frequent and more effective in raising sputum; strength increased; support worn 2 weeks.
C. W.	Bronchiectasis (dur., 5 years)	Dyspnea on walking; paroxysmal dyspnea; cough and expectoration; loss of weight	Striking general improvement; dyspnea decreased; no paroxysmal attacks; expectoration and cough decreased; 4 kg. gain in weight; can walk easily without dyspnea; support worn 4 weeks.
A. S.	Bronchiectasis (dur., 4 years)	Dyspnea; racking cough; difficult expectoration	Breathes more easily; expectoration facilitated; support worn 6 weeks.
H. M.	Bronchiectasis (dur., 7 years)	Dyspnea; cough; difficult expectoration; pain in abdomen	Dyspnea decreased; expectoration facilitated; pain in abdomen due to former racking cough stopped; support worn 3 weeks.
H. W.	Bron. asthma; ch. bronchitis; emphysema (dur., 6 years)	Marked dyspnea; paroxysmal dyspnea and cough; pain in abdomen	Striking general improvement; dyspnea decreased; attacks less frequent; cough less severe; support worn 6 months; died suddenly from coronary thrombosis; aged 69.
V. Mc.	Bron. asthma; ch. bronchitis; emphysema (dur., 4 years)	Cough and expectoration; dyspnea on exertion; pain in abdomen	Cough and expectoration decreased markedly; no dyspnea on walking; all-day cure and exercise; support worn 2 weeks.
G. E.	Ch. bronchitis; emphysema (dur., 7 years; glassblower, 21 years)	Dyspnea, especially lying on left side; "difficulty in releasing air;" paroxysmal dyspnea; cough	Dyspnea and cough decreased markedly; can lie on left side; support worn 1 week.

ports in 18 patients are shown in the accompanying table. In the remaining number the results were inconstant and tabulation was not attempted. Discomfort occurred in 4 thin patients; there was some question of extension in 3 tuberculous patients and the supports were removed. Of special interest is the decrease of dyspnea, cough, expectoration, fatigue and pain in the abdomen. This was striking in patients with severe racking cough and difficult expectoration. In some instances the improvement was reflected in expressions of comfort on the face. Exercise was started or increased in patients who experienced marked symptomatic relief. This occurred without discomfort and usually a request was made for additional exercise. Objectively there was a definite limitation in the expansion of the abdomen and a relative increase in the horizontal movements of the thorax. This was less marked in bed patients. In a few instances a striking reduction in the number of coarse râles in the lungs was noted. The roentgenogram of the chest showed elevations of the diaphragm varying from 1 to 3.5 cm.; the excursions were usually limited in extent (Figs. 2A and B; 3A and B). Especially striking was the decrease in the upward "rush" and "rebound" of the diaphragm in uncontrolled inspiration and expiration as in cough. Several roentgenograms indicated decreased illumination of the lungs. The vital capacity determinations showed a reduction from 5 to 20%. After the supports were worn for a few days the percentage returned to within 5 to 10 points of the original figure. This suggested that the breathing space in the lungs was reduced at first as a result of compression from the diaphragm and later increased as a result of greater thoracic expansion. No attempt was made to evaluate the changes in the lungs *per se* since a larger group should be studied critically over a long period of time. It is merely noted that in 4 tuberculous patients one large cavity disappeared and three decreased more than 2 cm. in diameter.

The present study indicates that abdominal supports may be useful for the relief of symptoms in various pulmonary diseases. In a number of instances, the results were more striking than would occur ordinarily from the use of "anti-spasmodic" and "expectorant" drugs. Although the effects of healing were not considered, the impression was received in certain tuberculous patients that the processes had become quiescent. This was suggested chiefly because in spite of exercise there was an increase in strength and gain in weight. However this may be regarded as an index of abeyance, there was no doubt that certain patients "carried" their infections with less general disturbance.

Various explanations for the findings may be considered. These are: that the elevated and restricted motion of the diaphragm favors rest for the lungs by distributing lung excursions somewhat evenly over different planes; the mechanism of breathing is effectively regulated due to improved coördination between diaphragm and thoracic movements; the "cushioning" effect from the secure abdom-

inal wall prevents a sudden "rebound" of the diaphragm following cough and thus reduces lung trauma; the long upward "rush" of the diaphragm due to negative pleural pressure is reduced; the removal of diseased tissue products, especially from the basal areas of the lungs is facilitated. In considering the mechanism of diaphragm elevation an illustrative comparison may be made between a perfect automobile inner tube and one with an area of thin rubber. On filling, the expansion of the perfect tube is approximately equal throughout. With the imperfect tube there is a "bulge" in the area of thin rubber. This appears before stretching occurs in other parts. In forcing air from the tube by compression the imperfect part will swell, as occurred in filling, which delays the passage of air. These features are comparable with the diseased lung as to its emptying and filling efficiency. In the patient with loss of weight or relaxed pendulous abdomen, the diaphragm is lowered and perhaps weakened. Furthermore the excursions are not well coordinated. This favors retention of air and secretions in the dependent parts of the lungs. An additional factor occurs in advanced basal disease, especially emphysema, in which the accessory muscles of the thorax play an important part in expiration. This tends to hold the diaphragm in a "flattened" position and the air and secretions are "locked" in the bases of the lungs. The inefficiency of the diaphragm is shown in its failure to compress the lungs from below upward. This corresponds with the "bulge" mentioned in the parallel drawn of the thinned area of the rubber tubing. Whereas the diaphragm is normally vigorous in function, it becomes in malnutrition and pulmonary disease a relatively weak and inefficient structure. Dr. McCrae's<sup>4</sup> use for many years of abdominal binders to reduce the discomfort in whooping cough supports the thesis of this study. Furthermore, patients with extreme dyspnea have discovered that comfort is obtained in the sitting posture with the body bent over the knees. These observations are similar to the observation of Alexander and Kountz<sup>3</sup> that 1 of their patients with emphysema breathed more easily when resting on his hands and knees or when wearing an abdominal support. These effects were due largely to the elevated and restricted movements of the diaphragm.

While the present study suggests that abdominal compression may be of value in the treatment of pulmonary diseases, there are no conclusions that it exerts a specific influence on the pulmonary lesions. The effects are regarded essentially as symptomatic responses. Apart from the value in treatment the supports may be useful in "testing" the effects of diaphragm elevation preliminary to proposed phrenicectomy, as was suggested in a personal communication from Dr. Henry A. Christian.

**Conclusions.** 1. The mechanism of diaphragm elevation has been studied with special reference to the occurrence of pulmonary symptoms in tuberculosis, bronchiectasis and emphysema associated with pneumoconiosis, chronic bronchitis and bronchial asthma.

2. The data suggest that a close relationship exists between the exaggeration of manifestations and the diaphragm operating at low levels with deep and uncontrolled excursions.

3. It seems possible that certain unfavorable results observed in the standard treatment of pulmonary diseases are due to inefficient diaphragm action. This may explain the occurrence of certain untoward effects attributed previously to the natural events of disease or to some special procedure.

4. It has been observed in certain patients that elevating and limiting diaphragm excursions by means of special abdominal supports facilitates expectoration, decreases cough and dyspnea, and influences most favorably the general condition.

5. The use of special abdominal supports is recommended as a supplementary measure in the management of pulmonary diseases.

Thanks are given to Dr. Leslie P. Anderson for assistance in the Roentgen ray studies, to Mr. Robert J. Titherington for assistance in making the silhouettes, and to Mrs. Millicent H. Maull for helpful cooperation in many ways.

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## THE TREATMENT OF TETANUS IN THE HOSPITALS OF LANCASTER, PA., OVER A PERIOD OF 30 YEARS.

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TETANUS as a clinical entity has been recognized by the medical profession at least since the time of Hippocrates (460 to 375 B.C.) who mentioned the fatality of "spasm supervening upon a wound." Since the discovery of the tetanus bacillus and the production of a prophylactic serum great progress has been made in the prevention of the disease. However, much remains to be accomplished in the matter of successful treatment of established cases.

The purpose of this paper is to present a survey of the results obtained by various methods of treatment in Lancaster County over a period of 30 years. We have examined the records of this

disease in the two hospitals of Lancaster since 1903. In the first decade 1903 to 1913, there were 12 cases, from 1913 to 1923, 33, and from 1923 to 1933, 51. Because of the well recognized and startling symptoms of the disease and the generally accepted use of serum in treatment we believe that the hospital cases we have reviewed includes the majority of the actual cases of the disease in the county for the last decade. During the first two decades serum was less regularly employed and patients with tetanus were not hospitalized as regularly as today.

Lancaster, in southern Pennsylvania, is in one of the regions where tetanus is most prevalent.<sup>1</sup> Practically all of Lancaster County is under cultivation, with truck farming as a major industry. The ground is heavily fertilized with manure, and much of the farming is done by hand. These are doubtless factors in the prevalence of the disease in this locality.

In the past 30 years we have record of 96 cases treated for tetanus in the Lancaster General Hospital and the St. Joseph's Hospital. Of the entire series of 96 cases there were 55 deaths (57 per cent). We have been unable to find statistics published in any other locality covering a similar period of time for comparison, but judging by combined reports from various regions over shorter periods of time, it would seem that the mortality in these two hospitals has been about the average or perhaps slightly below. In our group of 96 cases, of the 11 who received no antitoxin, 3 recovered (mortality of 72 per cent). Of the 85 who received antitoxin, 47 died (mortality of 56 per cent). To compare with these figures, Lanphear,<sup>2</sup> of St. Louis, reported in 1899 that the cases treated without serum had a mortality rate of 80 per cent, and Bloom,<sup>3</sup> of New Orleans, stated that the mortality rate antedating the full use of serum was 85 per cent. The small number of cases we have on record treated without antitoxin does not give a sufficient basis for definite conclusions, but it gives us some slight idea of how the results obtained in Lancaster compare with those in other localities.

In our series, statistics based upon the amount of antitoxin given in each case seem to be useless because usually the size of individual doses was about the same, but in very severe cases the patient died after receiving only 1 or 2 doses, making the total amount of antitoxin very low. If the patient lived, the antitoxin was invariably continued over a long period of time and the total amount administered was, therefore, very high. The total amount of antitoxin per individual case in this series ranged between 5000 and 500,000 units (average, 71,000). In order to give some idea of results obtained by the administration of varying amounts of antitoxin we have calculated the amount of antitoxin given during the first day of hospitalization in each case. The amount of antitoxin given in the first few hours did not seem to depend so much upon the severity of the patient's symptoms, as upon the dose customarily ordered

by the attending physician. The amount most frequently given the first day was 10,000 to 20,000 units. The mortality statistics arranged in accordance with the varying doses of antitoxin for the first 24 hours is shown in Table 1. Up to 40,000 units there seems to be a very definite decrease in mortality with increase in initial dose; beyond this point, the reverse is true. However, since only a few cases received these very large doses, accurate deductions are impossible. It is difficult to gauge the severity of each case

TABLE 1.—MORTALITY AND AMOUNT OF ANTITOXIN USED.

Units of antitoxin administered in the first twenty-four hours.	No. of cases.	Died.	Mortality, per cent.
5,000 or less . . . . .	13	8	61
10,000 . . . . .	14	9	64
12,000 to 15,000 . . . . .	10	6	60
16,000 to 20,000 . . . . .	22	10	46
25,000 to 30,000 . . . . .	6	2	33
40,000 . . . . .	8	2	25
50,000 . . . . .	4	3	75
50,000 to 100,000 . . . . .	8	7	88
Total cases receiving antitoxin . . . . .	85	47	55
Total cases receiving no antitoxin . . . . .	11	8	72
Total cases reported . . . . .	96	55	58

from the intern's history, and it is questionable whether or not these large doses were given because of unusually severe symptoms. It is also difficult to ascertain whether death resulted from the acuteness of the disease or whether the amount of antitoxin given may have had some influence upon the outcome.

The results obtained by various methods of administration are shown in Table 2. The high mortality of the 9 intravenous cases (88 per cent) is, of course, based on a very small group for statistical

TABLE 2.—MORTALITY AND ROUTE USED FOR ANTITOXIN.

Route of administration of antitoxin.	No. of cases.	Died.	Mortality, per cent.
Intramuscularly . . . . .	43	24	56
Intravenously . . . . .	9	8	88
Intramuscularly and intravenously . . . . .	14	2	15
Intraspinal, combined with any other method . . . . .	19	13	68
Total cases receiving antitoxin . . . . .	85	47	55
Total cases receiving no antitoxin . . . . .	11	8	72
Total cases reported . . . . .	96	55	58

value. The low mortality of the 14 cases who received mixed intramuscular and intravenous serum (15 per cent) should be noted. In examining the charts of the 19 cases receiving intraspinal combined with other forms of treatment, they do not impress one as having had more severe symptoms than the others, while the mortality rate (68 per cent) compares very unfavorably with the total

mortality rate of those receiving antitoxin (55 per cent). Furthermore, of the 13 patients who died after intraspinal antitoxin, 5 succumbed within 6 hours following the intraspinal injection. We have record of only 1 of the 13 having died in convulsions as did the majority of the other patients who died of tetanus. This raises the question of the safety of administering tetanus antitoxin intraspinally. In several cases it was impossible to ascertain whether a volume of cerebrospinal fluid equivalent to the volume of antitoxin given was withdrawn before the antitoxin was administered, but in some instances the quantity of cerebrospinal fluid removed was definitely stated and was certainly sufficient to avoid danger of increased intracranial pressure. In a small group of 4 cases, antitoxin was injected around the wound of entrance and into the trunk of the nerve supplying the area. Of these 4 cases, 3 recovered.

The period of incubation is said to be a very important factor in prognosis. Of the 4 cases developing tetanus within 5 days after the occurrence of the wound of entrance, 25 per cent died. Of the 37 patients developing tetanus in 5 to 10 days after the injury, 68 per cent died. Of the 17 patients developing tetanus 10 to 15 days after the injury, 53 per cent died, and of the 5 patients who developed tetanus more than 15 days after the injury, 46 per cent died. Thus in our series the highest mortality was found in those patients who developed tetanus between the 5th and 10th days after injury. This corresponds with a similar statistical report published by Osler<sup>1</sup> in 1907.

We were unable to arrive at any conclusion as to the influence of prompt treatment on mortality. In most cases treatment by tetanus antitoxin was instituted very soon after the admission of the patient to the hospital, but it is impossible to obtain from the charts any accurate idea as to how many hours before admission the first symptoms of tetanus appeared.

As to the frequency of the occurrence of tetanus in various ages, our 96 cases are divided as follows: 37 cases occurred in the first decade, 25 in the second, 8 in the third, 6 in the fourth, 7 in the fifth, 9 in the sixth and 4 in the seventh. Probably the frequency of occurrence in the first two decades is explained by the use of cap guns and fireworks, the habit of running about barefoot with open wounds of the feet, and the fact that smallpox vaccinations are made within this period.

A glance at the commonest wounds of entrance of the bacillus is enlightening (Table 3). Of the 10 that followed vaccination (10.4 per cent) with 6 deaths, we believe that the cases were due not to contaminated vaccine, but to soiling of partially healed vaccination wounds. The basis of this belief is the length of time elapsing between vaccination and the appearance of symptoms. In 2 cases we have no record of the date of vaccination. In 1 case a period of 10 days elapsed between vaccination and the appearance



of symptoms. In 6 cases the symptoms appeared 3 weeks after vaccination, and in 1 case, 1 month after vaccination. In several instances there is a statement on the history chart that the child was playing outdoors and injured the vaccination wound. A sterile dressing for the developed vaccine "take," similar to that applied to any other open wound, we believe should materially lower the incidence of tetanus. A tetanus toxoid is in the process of preparation at the present time which may prove of value when used in conjunction with vaccination. The commonest wound of entrance was the "splinter" wound (13 instances). The probable reason for the frequency of tetanus occurring in these cases is that the wound is ignored because it is so slight. Furthermore, a splinter wound provides the ideal anaërobic conditions for the growth of the tetanus bacillus. Of the 2 postpartum cases both patients died. One fatal case occurred following the injection treatment for hemorrhoids. In spite of the fact that other investigators have reported many cases following head injuries, in our series there were only 3 such cases. In 8 cases, no history of antecedent injury was obtained.

TABLE 3.—MORTALITY AND WOUND OF ENTRANCE.

Wound of entrance.	No. of cases.	Died	Mortality, per cent.
Lacerations . . . . .	21	12	57
Various kinds of abrasions . . . . .	19	11	57
"Splinter" . . . . .	13	7	54
Vaccination . . . . .	10	6	60
Puncture wounds . . . . .	9	5	55
Powder burns . . . . .	4	3	75
Other burns . . . . .	1	1	100
Postpartum . . . . .	2	2	100
Blisters on feet . . . . .	1	1	50
Compound fractures . . . . .	3	2	66
Injection of hemorrhoids . . . . .	1	1	100
Abscessed teeth . . . . .	1	0	0
Injury to middle ear . . . . .	1	0	0
"Sore throat" . . . . .	1	0	0
No history of wound . . . . .	8	4	50

Of the 96 cases, only 14 occurred within the city of Lancaster. The others occurred in rural districts or in small suburban towns.

At least 1 and probably more of this series of 96 cases received a prophylactic dose of antitoxin within 2 weeks of the onset of symptoms, but accurate information on this point could not be obtained.

Of this entire group of cases 4 might be classed as mild cases, showing only rigidity of the jaw, irritability, etc., but no convulsions. The remaining cases could all be classed as severe, and the occurrence of severe convulsions was noted on 69 of the case records.

**Summary.** Data compiled from the records of 96 consecutive tetanus cases treated in the two hospitals of Lancaster over a period of 30 years is presented.

In our series, the patients who received intraspinal serum in conjunction with any other route of administration showed a mortality of 68 per cent, although the total mortality for all cases including the 11 who received no antitoxin, was only 58 per cent. The patients treated with intraspinal serum apparently had no more severe initial symptoms than those not so treated and we, therefore, believe that intraspinal tetanus antitoxin administration affords very questionable safety. It is interesting to note that in the small series of 14 cases who received mixed intramuscular and intravenous serum the mortality was only 15 per cent.

We were surprised to find that tetanus as a sequel to vaccination comprised 10.4 per cent of the total number of our cases. We believe that these cases were not due to contaminated vaccine but rather to improper care of the wound after vaccination. The most common wound of entrance was the "splinter," which caused 13 per cent of our cases.

The highest mortality was found in those cases who developed symptoms between the 5th and 10th day after injury.

Although one cannot draw definite conclusions from a small group, our series seems to indicate that the ideal dose of antitoxin in the first 24 hours is between 25,000 and 40,000 units. At least, doses less than 20,000 units in the first 24 hours would seem inadequate.

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### A MODIFIED MERCURIC CHLORID REACTION (TAKATA-ARA) IN CIRRHOSIS AND IN NEOPLASMS OF THE LIVER.

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THE problem of distinguishing, particularly in late stages, liver cirrhosis from neoplasm, and certain other liver disturbances is often a very difficult and confusing one. Any procedure which renders this distinction more clear is therefore worthy of interest. The Takata-Ara test for establishing the diagnosis of liver cirrhosis has not as yet been investigated and reported in the American literature. The few reports in the European publications indicate that the test is of a high degree of specificity in this disease. The relative

simplicity of the performance of this test, together with what appears from reports to be its value, prompted its investigation in this clinic.

The test considered was originally proposed by Takata<sup>1</sup> and later by Takata and Ara<sup>2</sup> in 1925 as a colloid reaction in chest fluid, which would be useful in distinguishing between lobar and lobular pneumonia. They believed that it is the decreased stability of the serum proteins of the colloid system which makes precipitation with the mercuric chlorid-fuchsin solution possible. This they believed to be due to increased globulin. Necole<sup>3</sup> also concludes that the precipitate is due to a globulin effect. He believes that its albumin fraction exerts a protective action which opposes precipitation. In 1929, Staub<sup>4</sup> suggested that this colloid reaction if applied to blood serum might aid in determining the presence of liver cirrhosis. He based his suggestion on the probable alteration of the serum protein values in this disturbance. Jezler<sup>5</sup> investigated a series of cases and was able to add considerable confirmatory evidence to this suggestion. His original work was carried further in subsequent observations<sup>6</sup> in which the serum albumin-globulin relationship was studied. On the basis of the various studies certain explanations of the mechanism of the reaction have been advanced, and these will be subsequently discussed in brief.

*Material.* Studies were made upon the following: liver cirrhosis, 21 cases; hemochromatosis, 1; leukemia, with atypical cirrhosis, 1; early liver cirrhosis, 4; neoplasm involving the liver (secondarily), 6; acute yellow atrophy, 2; infectious and catarrhal jaundice, 5; toxic jaundice (chrysarobin-arsphenamin), 2; cholecystitis and cholelithiasis, 7; congenital hemolytic icterus, 2; liver abscess, 1; and miscellaneous disorders, which are catalogued in the table, 25 cases. The results in the series studies are shown in the tables. No attempt has been made here to report on entirely normal individuals, as this has been completely investigated by Jezler<sup>5</sup> with entirely negative results, which will, therefore, serve as sufficient control for cases herewith presented.

*Method.* Reagents: 0.9% sodium chlorid solution; 10% sodium carbonate solution; 0.5% mercuric chlorid solution; 0.025% aqueous fuchsin solution.

Into each of a row of 8 small glass tubes (those used for determining blood hemolysis are quite suitable) is placed 1 cc. of 0.9% sodium chlorid solution. To the first tube is added 1 cc. of blood serum, ascitic or other fluid. From the mixed content of the first tube 1 cc. is transferred to the second, the tube shaken, then 1 cc. transferred from Tube 2 to Tube 3, and this procedure is continued throughout the series. In the 8th tube the 1 cc. removed is discarded. The dilution of the serum or other fluid then ranges from 1 to 2 in the first tube to 1 to 256 in the last. To each tube is then added 0.25 cc. of the sodium carbonate solution and 0.3 cc. of the freshly prepared Takata reagent, which consists of a mixture of equal parts of the mercuric chlorid and aqueous fuchsin solutions. Readings are made immediately, and at  $\frac{1}{2}$ -hr. and 24-hr. intervals. They depend entirely on the precipitate in the tubes. The precipitate at the end of 24 hr. is almost invariably the most definite and constant, since precipitate which appears at earlier

readings frequently diminishes or disappears on standing. Clouding and color changes are without importance; the same is true of the blue granular precipitate that sometimes occurs in the tubes of highest dilution, *i. e.*, the 7th and 8th.

In view of the fact that we are concerned only with precipitation and that color changes play no part in our reading, we have found it possible to omit the fuchsin. A further slight modification is the use of 6 tubes, rather than 8; for as previously mentioned, the precipitate in the last 2 tubes is without significance, and often occurs in distilled water alone.

The readings are made as minus (no precipitate); 1+, 2+, or 3+. Charting is of convenience, as shown in Fig. 1. After moderate practice, charting is unnecessary and readings are negative, positive, or, for the sake of comparison in cases that are followed progressively, strongly positive.

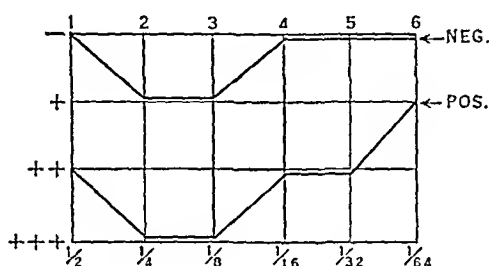


FIG. 1.—Typical negative and positive precipitation curves.

The standard by which positive reactions are judged is the appearance of a definite precipitate in 2 of the first 3 tubes, and at the same time a precipitate in any number of the following tubes, with the exceptions as previously noted. Positive reactions are usually quite characteristic, and negatives may have no precipitate in any tube, or a 1+ or a 2+ in any of the tubes from 4 to 7 alone. Figure 1 illustrates a typical negative, and a positive reaction curve. The latter curve may vary in form, but the variations are usually well on the positive side.

Blood if freshly collected must be centrifuged; due care must be exercised to prevent hemolysis, as it is possible that this may cause false positives. The presence of bile is without influence. Blood or other fluids may be preserved almost indefinitely on ice or with toluol. Ascitic fluid that contains blood or pus must also be centrifuged.

**Results. Cirrhosis.** The results obtained in this investigation agree very well with those of Jezler (Table 1). In the first group of 21 cases of advanced portal cirrhosis (Laennee) there were 20 positive reactions in both serum and ascitic fluid. The 1 negative case in this group was not seen in the clinic, the blood being examined only once. The diagnosis of cirrhosis had, however, been made upon good clinical grounds, and for this reason the case was included. In 1 case of hemachromatosis the reaction was strongly positive. The patient with myeloid leukemia has been reported more completely elsewhere;<sup>7</sup> he presented at autopsy a definite myeloid infiltration of the liver with an atypical cirrhosis, as well as what appeared to be old intrahepatic portal thrombosis. In the positive cases followed progressively to exitus the reaction did not in any case tend to diminish in degree of intensity, but as the terminal

stage of the disease appeared, the intensity of the reaction as judged by the amount of precipitate tended rather to increase. Esophagoscopy was performed on all but 1 of these cases with the Henning modification of the Wolff esophagoscope, to determine the presence or absence of esophageal varices, and gave positive findings in each instance. In 4 of the cases not coming to autopsy, laparoscopy was done by means of Henning's laparoscope through a small abdominal incision, to visualize the liver as an additional diagnostic measure. In the 4 cases described as "early liver cirrhosis," the patients all had fairly long histories of alcoholic overindulgence; livers were moderately enlarged and rather firm; all showed an increased urobilinuria. Three of the patients had gastric anacidity, and 2 had a moderate erythremia, with red blood counts ranging between 6 and  $6\frac{1}{2}$  million. None had ascites. The reaction was negative in all, and would therefore appear to be without value in these early cases.

TABLE 1.—RESULTS IN PORTAL CIRRHOSIS AND ALLIED CONDITIONS.

	No. cases.	Bichlorid test positive.		Esophageal varices.	Autopsy.	Operation.	Laparoscopy.	Other diagnoses.
		Serum.	Ascitic fluid.					
Advanced portal cirrhosis . . . . .	21	20	20	20	11	2	4	Lues (6) Dia- betes (2)
Hemochromatosis with cirrhosis . . . . .	1	1	1	..	1			
Leukemia with atypical cirrhosis . . . . .	1	0	0	0	1			
Early portal cirrhosis . . . . .	4	0	0	0	0			

*Liver Neoplasms.* The reaction was negative in all 6 cases (Table 2). All were cases of secondary liver tumor, the primary growth being gastric carcinoma in 3, peritoneal carcinoma in 1, lung carcinoma in 1, and an abdominal sarcoma in 1. Five of the 6 patients had very marked hepatic enlargement and 3 had marked ascites. It would appear that in this type of case the reaction is of particular value in clarifying the diagnosis.

*Other Liver Conditions.* Of chief importance were 2 cases of acute yellow atrophy. The first, man aged 58, was deeply jaundiced and obviously quite ill for a period of 2 months, during which time he lost much weight. The reaction was positive during the course of his illness, but he improved spontaneously, and rapidly regained weight and strength. His jaundice disappeared, and the reaction was negative on discharge. The second case, a man aged 45, was deeply jaundiced over a period of 7 weeks, and died in coma. Diag-

nosis at autopsy was "acute yellow atrophy." The mercuric chlorid test was positive on all 4 estimations made during his stay in the hospital. We felt that the condition of these 2 patients was essentially the same, and that the reaction would seem to be of value in distinguishing this condition from simple catarrhal jaundice.

TABLE 2.—RESULTS IN NEOPLASMS, ACUTE AND CHRONIC LIVER DISTURBANCES AND CONTROL CASES.

	No. cases.	Bichlorid test positive.	
		Serum.	Ascitic fluid.
Neoplasms . . . . .	6	0	0
Acute yellow atrophy . . . . .	2	2 (1-)	0
Jaundice . . . . .	18	0	
Other disease cases used as controls	26	0	
Infectious . . . . .			1
Catarrhal . . . . .			5
Toxic . . . . .			2
Abscess . . . . .			1
Cholecystitis cholelithiasis . . . . .			7
Congenital hemolytic icterus . . . . .			2
C. N. S. lues . . . . .			1
C. V. lues . . . . .			1
Nephritis . . . . .			4
Arteriosclerosis . . . . .			3
Thyrototoxicosis . . . . .			1
Polyserositis . . . . .			1
Lobar pneumonia . . . . .			2
Acute pulmonary tuberculosis . . . . .			10
Hypertensive heart disease . . . . .			3

The 18 cases with jaundice as the outstanding symptom were of significance in that they include a number of conditions that might be thought to render the reaction positive. Jaundice in these cases varied in duration from 1 to 10 weeks, and in intensity from moderate to very marked. There was some degree of hepatic enlargement in the majority of these patients, though this was transitory. Both in this group and in the others it was observed that the galactose tolerance test often bore no relation to the Takata-Ara reaction, the former quite frequently indicating hepatic functional impairment, while the latter was entirely negative. On the other hand, in cases of advanced cirrhosis with strongly positive Takata-Ara reactions, the galactose tolerance was normal. One case was examined in an acute hemolytic crisis, at which time the blood serum was quite red. Despite this, however, the reaction was consistently negative.

*Non-hepatic Diseases.* The final group represents a variety of pathologic conditions, which were examined chiefly as a means of control. Jezler<sup>5</sup> reports cases of nephritis, in which positive reactions were obtained; our cases were negative. Pongor<sup>8</sup> reports as high as 90% of positive reactions in patients with active pulmonary tuberculosis. In our 10 cases of active pulmonary tuberculosis in various stages of the disease, the reaction was entirely negative.

**Discussion.** Our results suggest certain possible causes for the production of a positive reaction: (1) extensive liver damage with the release of liver proteins (acute yellow atrophy) into the circulation; (2) an inability on the part of the liver to alter proteins that are contained in the blood; (3) the fact that some blood fails to pass through the liver, but passes directly from the splanchnic to the general circulation by way of collateral venous anastomoses. Certain phases of this problem are now under investigation in this clinic. The purpose of the present work has been to examine further the clinical application of this test.

**Conclusions.** 1. The application of a mercuric chlorid test (Takata-Ara) as an aid in the diagnosis of liver cirrhosis has been studied.

2. The results obtained confirm those of previous investigators as to its value.

3. Certain slight modifications are suggested for its performance.

4. The test is positive only in advanced cirrhosis, and is therefore of little value from the standpoint of early diagnosis.

5. Its chief worth lies in its differential diagnostic value to distinguish between cirrhosis and various liver neoplasms and other advanced liver disturbances.

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#### Addendum to article on The Effect of Leukocytic Cream Injections in the Treatment of the Neutropenias.

By MAX M. STRUMIA, M.D., Sc.D.

Since the completion of the article recently published in this Journal (187, 527, 1934), 3 more cases of malignant neutropenia have been treated with leukocytic cream.

## BOOK REVIEWS AND NOTICES.

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THE RENAISSANCE OF MEDICINE IN ITALY. By ARTURO CASTIGLIONI, M.D., Professor of the History of Medicine at the University of Padua. The Hideyo Noguchi Lectures. Publications of the Institute of the History of Medicine, The Johns Hopkins University, 3d ser., vol. 1. Pp. 91, 1 illustration. Baltimore: The Johns Hopkins Press, 1934. Price, \$1.50.

THE first of the Hideyo Noguchi Lectures and first volume of the third series of publications of The Johns Hopkins Institute of the History of Medicine presents an important topic in a worthy manner. Such scholarly but pleasantly written historical work is bound to help the reader to a truer understanding of Italy's medical greatness in the Renaissance. From Pietro d'Abano through Lionardo, to Berengario, Cesalpino, Colombo, Fracastoro and Galileo we get satisfyingly clear pictures of how these and lesser lights lived in relation to their times; but, as in his *Storia and Vollo d'Ippocrate*, the author is at his best in picturing vividly yet systematically the currents of medical thought that tumbled so boisterously yet constructively through the Italy of the 14th to 17th centuries. A delightful introduction by Sigerist shows us how this busy sanitation officer of a navigation company can do constructive scholarly work in the study and description of medical history.

E. K.

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THE MODERN TREATMENT OF SYPHILIS. By JOSEPH EARLE MOORE, M.D., Associate in Medicine, The Johns Hopkins University; Physician-in-Charge, Syphilis Division of the Medical Clinic and Assistant Visiting Physician, The Johns Hopkins Hospital. Pp. 535; 41 illustrations, Springfield, Ill.: Charles C Thomas, 1933. Price, \$5.00.

THIS book is a successful effort to make available, in concise form, the present knowledge concerning the most effective modern methods of treatment in all phases of syphilis. The author's conclusions are based on his experience with the Johns Hopkins material, aggregating some 18,000 cases, on an unsurpassed familiarity with syphilologic literature and on the findings of the Coöperative Clinical Group now being published in coöperation with the United States Public Health Service. These conclusions are presented in an extremely readable and direct manner, the text being supplemented by numerous tables and outlines, most of which are extraordinarily informative and to the point. While the author scrupulously indicates the many controversial aspects of syphilotherapy, he has not hesitated to express his preferences definitely, usually with the most cogent reasons. The book is personal in tone but avoids the didacticism and evidence of prejudice so commonly found in books on treatment.

The arrangement of the book falls roughly into three divisions—a consideration of the biology of syphilis and of the collateral factors affecting the patient and his family, chapters on the individual drugs used and chapters on the various phases of early and late syphilis. The decline of mercury treatment is emphasized by the devotion of only 9 pages to it. One is struck by the author's flat refusal to endorse the use of sodium thiosulphate in arsphenamin dermatitis. Much valuable and new material on the treatment of blood dyscrasias following arsphenamin administration is presented. The chapters on the treatment of early syphilis, of cardiovascular involvement, of syphilis of the eye, particularly optic atrophy, and of neurosyphilis would be worthy of monographic publication, and reflect the author's many truly original contributions in these fields.

Wherever possible, clearly outlined schemes or systems of treatment are



given, although the author recognizes the impossibility of routinization in many cases. The superiority of arspicnamine (606) in early syphilis is strongly emphasized. A representative bibliography is included with each chapter, the necessary inclusion of many of the papers of the author and his associates being an indication of the authoritative background from which the book springs. The index covers 50 pages and is extremely complete.

This presentation of a complex and controversial subject is clear and dispassionate terms is distinctly an achievement. The book will prove of value to specialist and practitioner alike and should do much toward more intelligent treatment of one of the most mistreated of all diseases.

D. P.

KREBS IM LICHTE BIOLOGISCHER UND VERGLEICHEND ANATOMISCHER FORSCHUNG. 1. Band: Ectodermkrebs. By MED. DR. JOS. LARTSCHNEIDER, Linz a. d. Donau. Pp. 192; 43 illustrations. Leipzig: Franz Deuticke, 1934. Price, Rm. 10.—

COMPARATIVE anatomic investigations lead the author to conclude that the human epidermis and the epithelial lining of the mouth, esophagus, stomach and upper part of duodenum are not of ectodermal genesis, but are the products of mesodermal elements (leukocytes, connective-tissue cells, phagocytes, etc.) forming a coating tissue (Mantelgewebe). He believes that regeneration of this tissue does not take place in the germinative basal layer as commonly assumed, but results from the immigration of nuclei of leukocytes, etc. Another of the many startling and unbelievable revelations characterizing this book refers to the incomprehensible fact that sometimes even minor appendiceal irritations produce quick perforation. This is attributed to the fact that the protostomal end of the gastrulic entodermal sac becomes later the appendix, in which the tendency to form an opening persists.

W. H.

ON PHASIC INTRODUCTORY AND RELEASE EFFECTS OF THE COCAINE GROUP ON VESSEL PREPARATIONS AND AN ATTEMPT AT A GENERAL APPRAISAL OF PHASE EFFECTS. By EDUARD RENTZ, Riga. Translated and Abstracted by LINN J. BOYD, M.D., F.A.C.P. Pp. 146; 14 illustrations, n. p., n. d. [New York, 1933.]

EXPERIMENTAL observations on the changing vasoconstriction and dilatation effects of certain anesthetics, barium and suprenen, their discussion, and literature pertaining thereto, occupy 41 pages. The remaining 92 pages contain a discussion of the theoretical possibilities involved in phasic phenomena, which are defined (in the translation) as "all transient and under certain conditions, reversely directed effects in spite of unaltered continuation of the stimulus, produced through various interferences and regardless of whether they have been evoked by the poison, its washing out or otherwise." An enormous literature (656 titles are listed in the bibliography) is cited to indicate to the author's satisfaction that phasic phenomena are not due to simple recovery, to tolerance, to "potential poisoning effects" (i. e., to concentration equilibrium between interior of cell and environmental solution) or to opposite effects of high and low concentrations of a drug (the so-called Arndt-Schulz rule). The conception of an "apparent increase in excitability," developed by Fröhlich and von Frey to account for similar phenomena in striated muscle, is not mentioned, although it appears to the Reviewer to furnish an adequate explanation with some experimental support. The author concludes that phasic phenomena are of the same general nature as the spontaneous rhythm displayed by all sorts of living matter, and are probably similarly caused by changes in state of protoplasmic colloids—a conception which

cannot, of course, be denied, but which means little because even in the case of indifferent narcotics, in spite of innumerable investigations and an enormous mass of valid evidence, the nature of the responsible change in protoplasmic colloids remains a matter of controversy. The author has too often selected fragments of evidence which suit his immediate argument and no attempt is made to evaluate the validity or relative importance of most of the evidence cited. The translation is literal, often awkward, occasionally imperfect. The Reviewer does not share the translator's opinion that this monograph is valuable or important. C. S.

**MENTAL HYGIENE IN THE COMMUNITY.** By CLARA BASSETT, Consultant in Psychiatric Social Work, Division on Community Clinics, The National Committee for Mental Hygiene, etc. Pp. 394; 1 illustration. New York: The Macmillan Company, 1934. Price, \$3.50.

MUCH has been written on mental hygiene by authors in many fields, but much of the writing has been limited to material related to one field. Usually such writings have been too indefinite for general use or have been largely propaganda. At least no publication in book form has appeared heretofore which classified mental hygiene as regards certain professions.

In this volume, however, the relation of mental hygiene is taken up in the field of medicine, nursing, social service agencies, parental education, pre-school child, teacher training, church, industry and from other important angles. The author aims not to present a brief for mental hygiene but to aid individuals, committees and communities, by presenting a panoramic sketch of how practical mental hygiene may be of importance and value. She fulfills this purpose well. Many good authorities are quoted and the huge amount of material has obviously been organized from reliable sources. The book is very easy reading. The material is presented in a very thoroughgoing manner. There is much detail, and the occasional redundancy is explained when we consider the numerous sections discussed.

An unusual feature is the presentation of questions and suggestions at the end of each chapter largely related to the development of mental hygiene in the particular field with which the chapter deals. This book will make an excellent text and reference book for communities and for professional people in general. It is not technical and not propaganda. It is simply a careful account of what mental hygiene actually is and what bearing it has on the lives and development of human beings. L. S.

**THE ANATOMY OF THE RHESUS MONKEY (MACACA MULATTA).** By Various Contributors. Illustrated by BENJAMIN KOPEL. Edited by CARL G. HARTMAN, Department of Embryology, Carnegie Institution of Washington, and WILLIAM L. STRAUS, JR., Department of Anatomy, Johns Hopkins University. Pp. 383; 125 illustrations. Baltimore: The Williams & Wilkins Company, 1933. Price, \$6.00.

THE increasing use of the rhesus monkey as a laboratory animal in recent years has emphasized the need for a handbook of the gross anatomy of this species. This has been met by the coöperative activities of 19 American anatomists in a manner so admirable that the book could well serve as a model for future projects of a similar character. In addition to a succinct but adequate account of the gross anatomy, there are useful chapters on the groups and names of macaques, and on growth and development, as well as an appendix giving the methods of housing and care of monkeys, based chiefly on the rich experience of Dr. Corner, of Rochester, and Dr. Hartman, of Baltimore. The illustrations, which are uniform, clear and excellent, are chiefly pen and ink drawings done by a single

artist, Mr. B. Kopcl. The Basle anatomic nomenclature, the standard for human anatomy, has been used, rather than the terminology of comparative anatomy. The book is a real contribution and the editors and other authors deserve both praise and gratitude. It will be of great use to the growing number of zoölogists, anatomists, physiologists and other medical scientists who use the monkey as a laboratory animal. E. C.

### NEW BOOKS.

*Allergy in General Practice.* By SAMUEL M. FEINBERG, M.D., F.A.C.P., Assistant Professor of Medicine and Attending Physician in Asthma and Hay Fever Clinic, Northwestern University Medical School; Professor of Medicine in the Cook County Graduate School of Medicine; Attending Physician, Cook County Hospital, Chicago. Pp. 339; 23 illustrations and a colored plate. Philadelphia: Lea & Febiger, 1934. Price, \$4.50.

*The Span of Life. As Influenced by the Heart, the Kidneys and the Blood Vessels.* By FRANKLIN R. NUZUM, B.S., M.D., F.A.C.P., Medical Director, Santa Barbara Cottage Hospital. Pp. 108; 9 illustrations. Springfield, Ill.: Charles C Thomas, 1933. Price, \$2.00.

"This book describes briefly, and in a manner understandable to the lay public, the functions of the heart, the kidneys and the blood vessels. The important changes that may occur in the structure of these tissues are shown and the causes of these changes, in so far as they are known, are given. It suggests measures for their prevention, and, once they become established, it outlines the management of these changes."

*Formes, Vie et Pensée.* By J. BEAUVÉRIE, and others. Pp. 419; illustrated. Lyon: Librairie Lavandier, n.d. Price, 20 fr.

*Das Wunder der Heilung durch eigenes Blut.* By DR. LUDWIG STERNHEIM, Pp. 64. Bern: Hans Huber, 1933. Price, Sw. Fr. 3.50.

A highly enthusiastic brief for autotransfusion, with a few case abstracts and an alphabetically arranged list of disorders in which it is recommended.

*The Harvey Lectures 1932-1933, Series 28.* Delivered under the Auspices of The Harvey Society of New York. By various contributors. Edited by DR. EDGAR STILLMAN. Pp. 233; illustrated. Baltimore: The Williams & Wilkins Company, 1934. Price, \$4.00.

*Bright's Disease.* A Clinical Handbook for Practitioners and Senior Students. By J. NORMAN CRUICKSHANK, M.C., M.D., D.Sc., F.R.F.P.S. (GLAS.), M.R.C.P. (LOND.), Senior Assistant to the Muirhead Professor of Medicine, University of Glasgow; Assistant Physician, Glasgow Royal Infirmary; Visiting Physician, Southern General Hospital, Glasgow. Pp. 208. Baltimore: William Wood & Co., 1933. Price, \$3.75.

*Cancer and Its Allied Diseases.* By WILLIAM F. KOCH, A.B., A.M., Ph.D., M.D. Pp. 308; illustrated. Detroit: By the author, 1933. (Price not given.)

A statement by the head of the Koch Cancer Foundation of his own views on cancer formation and its treatment by the Koch Cancer Foundation.

*Cold Spring Harbor Symposia on Quantitative Biology, Volume 1.* Pp. 239; illustrated. Cold Spring Harbor, L. I., N. Y.: The Biological Laboratory, 1933. Price, \$2.90.

*International Clinics, Vol. 1, Forty-fourth Series, 1934.* By various contributors. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore. Pp. 320; many illustrations, 1 in color. Philadelphia: J. B. Lippincott Company, 1934. (Price not given.)

A new feature inaugurated in this volume is a supplement of 2 clinical case studies from the Pittsburgh Diagnostic Clinic, offered in order "to afford practice in the formulation of a diagnosis. Accompanying postcards can be filled out with check requests for the procedures which you feel are definitely indicated." Two packets will be returned, one giving the information requested, the other a final report by the Clinic staff.

*Early Science in Oxford.* By R. T. GUNTHER, Vol. IX. *De Cordc* by RICHARD LOWER, London, 1669. With Introduction and Translation by K. J. FRANKLIN. Pp. 220; illustrated. Oxford: For subscribers at University Press, 1932. Price, £1, 1s.

*The Greek Herbal of Dioscorides.* Illustrated by a Byzantine A.D. 512; Englished by JOHN GOODYER A.D. 1655; Edited and First Printed A.D. 1933 by ROBERT T. GUNTHER, M.A., HON. LL.D. Pp. 701; 396 illustrations. Oxford: For author at University Press, 1934. Price, £3, 3s.

*The Surgical Clinics of North America. Volume 14, No. 1 (Philadelphia Number, February, 1934).* Pp. 226; 62 illustrations. Philadelphia: W. B. Saunders Company, 1934. Price, Paper, \$12; Cloth, \$16.

Students Aids Series. *Aids to Qualitative Inorganic Analyscs.* By R. G. AUSTIN, B.Sc. (LOND.), A.I.C., F.R.M.S., Associate of University College, Southampton Demonstrator, St. Thomas's Hospital Medical School; Lecturer on Chemistry at Wimbeldon Technical College, S.W. With an Introduction by R. H. A. PLIMMER, D.Sc. (LOND.), Professor of Chemistry in the University of London at St. Thomas's Hospital Medical School. Pp. 204. Baltimore: William Wood & Co., 1933. Price, \$1.50.

"This little book is an attempt to provide, in as small a compass as possible, a well-tryed system for the analysis of simple inorganic substances."

Students Aids Series. *Aids to Pathological Technique.* By DAVID H. HALER, M.B., B.S. (HONS.), Lond., Pathologist, Infants Hospital, S.W. 1; Battersea General Hospital, S.W. 11, etc. Pp. 187; 18 illustrations. Baltimore: William Wood & Co., 1933. Price, \$1.50.

"This book is an attempt to give the student and other laboratory workers some ideas as to methods which have been found to work best in actual practice."

Students Aids Series. *Aids to Neurology.* By E. A. BLAKE PRITCHARD, M.A., M.D. (CAMB.), M.R.C.P., Assistant Physician, Hospital for Epilepsy, Maida Vale; Assistant in Medical Unit, Neurological Department, University College Hospital, London. Pp. 376; 43 illustrations. Baltimore: William Wood & Co., 1934. Price, \$2.00.

"An attempt has been made to give a summarized account of the clinical conditions which most commonly result from disease of the nervous system."

Students Aids Series. *Aids to Botany.* By H. J. BONHAM, B.Sc., Biology Master, Crypt School, Gloucester. Pp. 221; 47 illustrations. Baltimore: William Wood & Co., 1934. Price, \$1.50.

"This book, uniform with other volumes in the Students' Aids Series, has been modelled on the syllabuses of examinations normally taken in the Sixth Form of (English) schools, or at the end of the first year at Universities and Colleges."

## NEW EDITIONS.

*Treatment in General Practice.* By HARRY BECKMAN, M.D., Professor of Pharmacology at Marquette University School of Medicine, Milwaukee. Pp. 889. Second edition, revised and entirely reset. Philadelphia: W. B. Saunders Company, 1934. Price, \$10.00.

Students Aids Series. *Aids to Anatomy.* By C. H. FAGGE, M.B., M.S. (LOND.), F.R.C.S. Pp. 333. Ninth edition. Baltimore; William Wood & Co., 1933. Price, \$2.00.

"This edition is couched in the new anatomical terms. A glossary of the most noticeable changes from the old terminology which was used in the eighth edition will be found on pp. 302-306 "

# PROGRESS OF MEDICAL SCIENCE

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## THERAPEUTICS

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UNDER THE CHARGE OF

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### THE TREATMENT OF ERYTHREMIA (POLYCYTHEMIA VERA).

ERYTHREMIA, since the clinical description by Osler<sup>1</sup> in 1903, has been considered a definite entity, but lack of understanding of its true etiology has made all treatment rather unsatisfactory. Two etiologic factors have been considered: (1) A malignancy of the erythrocytic tissue comparable to the disease of the lymphogenic or myelogenic tissue known as leukemia; (2) a disturbance in the hormonal control of the bone marrow.<sup>2,3</sup> This latter hypothesis has received considerable attention recently, due to the newer knowledge of the nature of pernicious anemia, a disease which in many respects presents an antithetical clinical and hematologic picture.

All successful forms of therapy have been directed toward reducing the number of red blood cells in the circulation and thus to relieve the two outstanding features of the disease, namely, increased blood volume and increased blood viscosity. The correction of these factors has been very successful in temporarily relieving the various symptoms and prolonging the life of the patient. It is questionable, however, whether the fatal termination of the disease is altered by therapy.

The problem of reducing the polycythemia and subsequently decreasing the total blood volume and blood viscosity has been attacked by two methods. The first is to reduce the erythrocytes in the circulating blood; this has been done by venesection and, to a greater extent, by the use of hemolytic agents. The second has been to reduce the activity of the erythrocytic tissue in the marrow, which is always in a hyperplastic state in the disease. Difficulties have arisen here because of the inability to obtain agents which can be easily controlled. If the dosage is too great, the erythrocytic tissue may be too greatly depressed or the platelets and leukocytes reduced to a dangerous degree.

The most widely used form of therapy today is phenylhydrazin.

This drug was first suggested for use in erythremia in 1918 by Eppinger and Kloss.<sup>4</sup> Recognized as a protoplasmic poison, as evidenced by experimental use of the drug in animals, it has proven very useful in erythremia. A normal erythrocyte count can be maintained in patients by phenylhydrazin given in therapeutic doses, without producing clinical liver or kidney damage, although when given to rabbits in large doses, it produces definite toxic destruction of these organs. This has been admirably demonstrated by Bodansky and coworkers in their study of the action of phenylhydrazin hydrochlorid and acetylphenylhydrazin. The chief effect of phenylhydrazin is to destroy erythrocytes, but it is possible that it also depresses the bone marrow to some degree.

One of the objections to phenylhydrazin hydrochlorid has been its tendency to produce toxic symptoms, even when used in very minute amounts. The most common of these are gastro-intestinal upsets, manifested by nausea, diarrhea, flatus, anorexia and abdominal cramps. Some patients complain of increased weakness and a feeling of pressure about the neck with this medication. This difficulty has been somewhat overcome by the introduction of acetylphenylhydrazin which, according to recent reports by Stone<sup>6</sup> and others, is as effective as phenylhydrazin hydrochlorid but does not produce toxic symptoms as readily.

The dosage of phenylhydrazin varies with the individual case. The usual procedure is to give the patient rather large doses, either daily or every other day, until the desired response is obtained. This is then followed by a maintenance dose that will keep the blood count at a normal level. If phenylhydrazin is given rapidly, there is a hemolytic crisis with jaundice and a rapid fall in the erythrocyte count. Better results are perhaps obtained if the drug is given more slowly and the hemolytic crisis avoided. Many have observed the rise in leukocyte count at the onset of the decrease in erythrocytes, but its value is doubtful as an aid in regulating the administration of the drug. The initial course should always be stopped before the desired erythrocyte count is obtained, because the drug has a cumulative action and may produce a severe anemia. The amount of the drug necessary to produce a normal erythrocyte count will vary considerably in each individual. This can only be determined by frequent blood studies and slow administration. A satisfactory procedure is to give the patient from 0.1 to 0.3 gm. every other day until the erythrocyte count approaches normal, then to put the patient on a maintenance dose. For some patients this will be as low as 0.1 gm. every 10 days, while others will require from 0.1 to 0.6 gm. weekly. Phenylhydrazin hydrochlorid and acetylphenylhydrazin require about the same dosage.

The organism does not seem to acquire a tolerance to the drug, though we may have a temporary phase of apparent tolerance ascribed to the increased resistance of newly formed erythrocytes. This is the explanation of the so-called tolerance as given by Bodansky. This phase is only temporary and, when there is a sufficient number of the mature cells in the circulating blood, there will again be a beneficial result from the drug. It is certain that equal doses given while the animal is still anemic will cause increasingly less blood destruction.<sup>7</sup> Some patients gradually require decreasing amounts of the drug after a

period of treatment. In a series of 37 cases reported by Griffin,<sup>8</sup> a few patients, after several years' treatment, were able to dispense with the drug completely. This may be due to the depressing effect of the drug on the bone marrow.

Phenylhydrazin should not be used indiscriminately, for there are several apparent contraindications to its use. Many have noted the development of thrombosis during the course of treatment. In a disease where thrombosis is so frequent, even in the untreated case, it is difficult to evaluate the rôle of phenylhydrazin in the production of this complication. With the increased blood destruction and rise in platelets that accompany phenylhydrazin administration, the tendency to thrombosis is probably temporarily increased. Because of this factor, Griffin and Conner<sup>9</sup> have pointed out that advanced cases requiring treatment in bed should not be given phenylhydrazin. Older patients with arteriosclerosis should be treated very cautiously with very small doses. The same is true in patients who have already developed thrombotic lesions. Patients confined to the hospital during treatment should not be kept in bed but should be allowed up and perhaps given massage, in addition, to keep the circulation active.

Irradiation (Roentgen ray, radium) has been used very extensively in erythremia, in many cases with very excellent results. The early reports were not as favorable as the more recent ones, due perhaps to the improved methods. Most observers agree that the best results are obtained by the use of depressing doses of the Roentgen ray over the long bones and chest. Irradiation of the spleen has given poor results. If the spleen is exposed at all, it should not have sufficient irradiation to depress its normal functions. With the therapeutic response from the depression of the marrow and the return of the erythrocyte count to normal, the spleen usually decreases in size.

The use of irradiation offers some difficulties. The dosage is difficult to regulate and the amount of depression of the erythrogenic tissue is not easily controlled. If the depression is marked, the patient may go into an anemic phase. This may be and is often accompanied by a depression of the leukocytes and platelets. To prevent such a complication during the course of irradiation, the blood should be followed closely and exposures stopped before the blood has reached the desired level; then, if more treatment is required, it can be given very cautiously. After a satisfactory course of irradiation, many patients have a prolonged remission lasting years, while others receive only temporary relief, necessitating a repetition of the course after a few months. Some patients, after an initial success, do not respond to subsequent irradiation.

In those cases with leukemia or pseudoleukemia combined with erythremia, radiation seems the most rational form of treatment. This has been used alone or combined with phenylhydrazin. It is likewise of value in patients who cannot be observed closely over a long period of time. Such patients must be watched during the period of exposure but, in the long remissions that may follow, frequent blood counts are not as necessary as with phenylhydrazin therapy. Such prolonged remissions have been observed by Milani,<sup>10</sup> who believes that the Roentgen ray is the best form of therapy available.

Venesection will produce very satisfactory temporary relief. The

effect, however, is very transient and the procedure has to be repeated frequently because it stimulates the bone marrow. However, in certain cases it has been found very useful for immediate relief of symptoms. It is also a safe procedure that may be used when conditions contraindicate the other accepted forms of therapy.

Opinions as to the value of spleen extracts vary. Lichtwitz and Franke<sup>11</sup> reported 2 cases with rapid fall in the erythrocyte count with spleen extracts and clinical improvement of the patient. The hemoglobin fell very little and slowly or may even rise, but the erythrocyte count became normal in 2 to 3 weeks. With cessation of the treatment the erythrocyte count rose again. There was apparent danger in the indiscriminate use of the extract, because anemia could be produced and frequent observations were necessary. The reports on the use of spleen extracts in this country have not been so favorable, the majority of observers having noted very little effect on the erythrocyte count. This may be explained by the observation of Kähler<sup>12</sup> that only a selected group of patients respond to the spleen extracts. The limited knowledge of the function of the spleen in a normal adult makes the rationale of this type of treatment questionable, but it is perhaps one that deserves further investigation.\*

Benzol has been used by many in the treatment of erythremia, but is being replaced by other forms of therapy. The drug definitely depresses the erythrocytic tissue of the marrow but apparently has a greater tendency to depress the myelogenous tissue.<sup>13</sup> With its use, a marked leukopenia may develop and even a true myelophthisis of the bone marrow. Minot<sup>3</sup> regards this drug as dangerous and of no value in the treatment of erythremia.

Arsenic has been used by several observers in erythremia without very striking results. More encouraging is the report given by Forkner<sup>14</sup> in his series of cases of erythremia treated with potassium arsenite (Fowler's solution). The results, although not as dramatic as the use of this drug in chronic myelogenous leukemia, are quite encouraging, in that it offers an agent which is relatively non-toxic, the dosage of which is easily controlled. The drug is administered by mouth and in the reported cases the fall in red blood cells began as early as 10 days after the initial administration in some cases, while in others the fall did not take place until after weeks of treatment. Fowler's solution is given by mouth, after meals, beginning with 3 to 4 minims 3 times a day and increasing daily in gradual amounts until the desired effect is produced or until a total of 17 to 20 minims 3 times a day is administered. Forkner recommends starting with 3 to 4 minims 3 times a day for 2 days, then increasing the daily dose by 3 minims; in 2 days the dosage is increased further at the same rate until the first sign of intoxication, anorexia, is noted. This usually takes place when the patient is receiving 24 minims daily. After this, the drug is increased very slowly by 1 minim daily; by this method the dosage can be increased to 12, 15 or 20 minims 3 times a day. Potassium arsenite, like phenylhydrazin, requires a maintenance dose after a normal erythrocyte count is once reached.

\* Numerous reports on the erythrocytic action of splenic extract would argue against the logic of this form of treatment, though it is, of course, possible that extracts prepared in different ways might have opposite effects.—EDITOR.



The vascular changes found in erythremia account for the majority of the symptoms. Those due to vascular distention and increased viscosity *per se* are relieved when the erythrocyte count has been reduced to a normal level. Those due to changes in the vessels themselves, such as thrombosis or endarteritis and a resulting infarction, present a greater problem in making the patient more comfortable. Not infrequently, such an accident brings the patient to a physician. The nature of these symptoms depends upon the location of the lesion, usually cerebral, abdominal or in the extremities. The last is quite common and the pain associated with such lesions is of chief concern to the patient. Such lesions not infrequently persist after the erythrocyte count is normal and require special treatment. Jacobi<sup>15</sup> reported immediate relief of symptoms in a case with peripheral arterial disease by the administration of physiologic saline solution intravenously. When the intravenous therapy was begun, the patient was also irradiated but, with the continuation of irradiation, the pain returned when the administration of the saline was stopped. Bernheim,<sup>16</sup> in 3 cases of erythremia with high blood viscosity, obtained a marked decrease in viscosity and symptomatic relief for at least 24 hrs. by the injection of 250 cc. of 2% buffered solution of sodium citrate. Other forms of therapy consist essentially of restoring the circulation by the development of collateral circulation.

In an attempt to find a more satisfactory form of therapy in erythremia, many procedures have been used which have proven ineffectual. Splenectomy was used and abandoned as unwise and useless. Barach and McAlpin<sup>17</sup> had 2 patients breathe 50% oxygen for a period of 2 weeks, with no significant decrease in the polycythemia. Rothman<sup>18</sup> used a high-fat diet, because of the hemolytic action of fatty acids, without significant results.

Recent hypotheses as to the etiology of erythremia suggest an entirely different approach in therapy. Several investigators have compared the symptomatology, physical findings and course of erythremia with pernicious anemia. Patton and his coworkers<sup>19</sup> have noticed frequently high gastric hydrochloric acid content and increased plasma cholesterol in erythremia and achylia and decreased plasma cholesterol in pernicious anemia. Both diseases have unexplained remissions. Several instances have been reported of patients with polycythemia developing anemia. Platt<sup>20</sup> studied a patient who, after developing erythremia, gave 39 transfusions over a period of 4 years and then developed an anemia with a low color index and typical glossitis, with improvement on liver therapy. This patient later developed the typical picture of erythremia. Minot and Buckman,<sup>21</sup> Klumpp and Hertig,<sup>22</sup> and others have studied patients who developed definite leukemic or pseudoleukemic phases during the course of the erythremia. This association certainly suggests a similar etiology.

Castle<sup>23, 24</sup> has demonstrated in normal gastric juice a substance which causes normal maturation of erythrocytes in patients with pernicious anemia. It is probable that pernicious anemia is caused by an insufficient elaboration of this principle. Morris<sup>25</sup> has designated this substance "addisin" and suggests that in patients with erythremia there is an oversecretion of addisin. The relation of erythremia to pernicious anemia then would not be unlike the relation of hyperthyroid-

ism to hypothyroidism. A similar hormone theory has been suggested by the work of Tuchfeld.<sup>26</sup> Morris suggests that a diet low in purin over a long period of time might be effective, in view of the fact that the sources of the hemopoietic substance effective in pernicious anemia have a high purin content (liver, kidney, stomach, nucleic acid). In support of the hormone theory, he reports a patient with erythremia and gastric ulcer who had frequent stomach lavages over a period of 6 months, with steady decrease in the blood count from 10 to 5.3 millions. When the lavages were discontinued, the erythrocyte count gradually increased to 10.2 millions at the end of 5 months.

The spontaneous remissions, which have been observed in erythremia, make the evaluation of any therapy difficult. The possible future isolation of a hormone, which is responsible for the increased activity of the erythrogenic tissue, may lead to a more rational therapy.

J. M. B.

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#### THE PHARMACOLOGIC PROPERTIES AND THERAPEUTIC APPLICATIONS OF ALPHA-DINITROPHENOL (1-2-4).

ALPHA-DINITROPHENOL (1-2-4) possesses striking pharmacologic properties. Recent observations have also revealed its therapeutic usefulness. The first systematic investigation of its biologic effects was conducted during the World War, as a result of observations of poisoning in munitions workers.<sup>1,2,3</sup> A more recent interest in the pharmacology of this substance has been revived by the systematic studies of

the fever-producing properties of nitrated naphthols by C. Heymans and his associates.<sup>4, 5</sup> Magne, Mayer and Plantefol,<sup>6</sup> Guerbet<sup>7</sup> and Tainter and Cutting and their associates<sup>8, 9, 10</sup> have undertaken a systematic study of the pharmacologic behavior of dinitrophenol. It was Tainter and Cutting, also, who first proposed its use in the treatment of obesity and in other conditions associated with lowered metabolism of the body.<sup>11, 12</sup>

**Toxicologic Observations During the World War.** The experiences gained during the World War, well described by Perkins,<sup>3</sup> have a particularly important bearing on the recently observed untoward therapeutic effects of dinitrophenol. The toxic effects of the explosives manufactured in Europe and the United States caused numerous fatalities among the workmen handling them. As far as dinitrophenol is concerned, it was thought at first that the toxic effect was due to some contamination. Soon it was found, however, that dinitrophenol itself, in the form of dust or vapor, may gain entry into the human body through the skin, the gastro-intestinal canal or the respiratory tract—the relative importance of these routes differing in various occupations. The skin was thought to be the most important portal of entrance in industrial poisoning.

*Subacute intoxication* usually manifested itself in anorexia with furred tongue, nausea, vomiting, diarrhea and colic. Rarely icterus was observed, due to the coloring properties of dinitrophenol, rather than to increased bile pigments. The workers often complained of weakness, loss of weight, headaches, and sweating. In *acute intoxication* the onset was sudden, usually with a sensation of intense fatigue, as if the circulation to arm and legs were "cut off." There was severe thirst, painful sensation of constriction at the base of the chest, agitation anxiety, dyspnea, elevation of the heart rate and fever. The urine was greatly decreased. In some instances of fulminating intoxication, death occurred within a few hours with general excitement and convulsions, followed by coma with unusually high temperature. Such a collapse developed at times while workers were walking home after a day of work without complaint. It was also noted early that in the fatal cases rigor of the body developed within 10 to 20 min. after death. A careful investigation by French and American observers soon established the fact that individual susceptibility played an important rôle in dinitrophenol intoxication, as only a limited number of workers developed intoxication under apparently identical conditions. Alcoholism, as well as the presence of albuminuria, has apparently predisposed to intoxication. There appeared to exist a relative susceptibility to dinitrophenol intoxication among white and a resistance among black workers.

Chemical studies have revealed that dinitrophenol changes partially or completely into its reduction products in the blood, tissues and urine. Among the reduction products found are: amino-2-nitro-4-phenol, amino-4-nitro-2-phenol, di-amino-phenol, and nitrogen compounds resulting from the combination of two molecules of amino-nitro-phenol, or of di-amino-phenol. Of these compounds the presence of amino-2-nitro-4-phenol indicates the presence of intoxication, and the demonstration of this compound in the urine is the basis of the violet reaction of Devrien.

Perkins<sup>3</sup> has also conducted *experiments* on horses, dogs, rabbits,

pigeons, turtles and frogs and has found that 0.01 gm. per kg. of body weight was toxic. All animals exhibited an exaggeration of their heat-radiation activities. He has pointed out that the fundamental phenomenon in all species of animals has been an extensive increase in the combustion of oxygen which is neither directly nor indirectly the result of stimulation of the nervous system. In experiments with *chronic intoxication* variable susceptibility was observed. All the animals lost weight. Perkins claims to have induced a tolerance in animals after repeated injection of non-fatal doses.

**Recent Pharmacologic Contributions.** As the experimental results of Belgian, French and American investigators<sup>4-10</sup> coincide in all the important aspects of the problem, they can be summarized as follows: Dinitrophenol is a yellowish-brown crystallin solid, only slightly soluble in water, or in physiologic saline solution. It can be dissolved up to 2% in ethylene or in propylene glycol. After the addition of about one-half its weight of bicarbonate of soda, it becomes soluble up to 3% in water. Such a solution of the sodium salt of dinitrophenol has a reaction of about pH 8.1 and is stable for years. The solution stains the skin and tissues. After its absorption it may produce a yellow color of the blood serum and of the sclera. The yellow color of the serum can be differentiated from the color of the bile pigment by the addition of 1 drop of 5% solution of hydrochloric acid, which absorbs the color of dinitrophenol, but not that of bile pigments.

Moderate doses affect all the species of animals tested in the same way. The first effect noted is an increase in respiration and in metabolism, present before there is any rise in temperature. In mammals, 5 mg. per kg. is the minimal and 20 to 30 mg. the maximal dose that induces fever. If higher doses are given, death may ensue before the temperature has reached its height (Tainter and Cutting<sup>8</sup>). The maximal febrile reaction after a moderate non-fatal dose occurs about 1 hr. after the subcutaneous or intramuscular injection. The fever may develop independently of the central nervous system and of the contraction of the stretched muscles, and is not prevented by ergotamin or by adrenalectomy and thyroidectomy.<sup>9</sup> If non-fatal doses are given, the effects subside usually 4 to 5 hrs. after the injection. Death in experimental animals may result from (a) direct circulatory depression, (b) hyperpyrexia, or (c) acidosis and anorexia.

Tainter and Cutting<sup>9</sup> have investigated the effect of repeated doses on the tolerance of the animal body to dinitrophenol. Administration of moderate doses at intervals of 3 or more days did not result in altered tolerance in 2 to 3 months. No evidence of toxic effects on the liver or other organs was found. The depression of the respiration induced by morphin, chloral, alcohol and barbital was counteracted by dinitrophenol. The efficacy of dinitrophenol was found to be comparable to that of caffein. The authors, however, pointed out that "the animals may still die, in spite of maintenance of adequate pulmonary ventilation." Dinitrophenol did not prevent death from just fatal doses of sodium barbital. It was found that the administration of physiologic salt solution and cooling by means of tepid baths exerted a partial antidotal effect.

Hall and others, in a subsequent study<sup>10</sup> investigating the effect of dinitrophenol on the metabolism and the circulation, found an elevation

of the oxygen consumption as early as 1 min. after the administration of dinitrophenol. After larger doses the oxygen consumption may amount to over tenfold the normal rate. The rise in the temperature is secondary to the increased oxygen combustion. There is a marked decrease in the liver and muscular glycogen, while the blood sugar and lactates tend to rise. The total carbohydrate disappearing has accounted for less than one-half the oxygen consumption; hence the principal fuel burnt must be other foodstuffs. The increased metabolism is maintained by increased minute volume output of the heart and by an increased arteriovenous oxygen difference.

**Therapeutic Applications.** The fact that animal experimentation has revealed that dinitrophenol, administered in relatively small doses, induces a considerable elevation of the basal metabolic rate without fever or other undesirable toxic manifestations, has suggested to Cutting, Mehrtens and Tainter its application in obesity and other conditions associated with low metabolism of the body. In their first clinical report,<sup>11</sup> they describe their observations on 8 patients to whom single doses of 3 to 6 mg. per kg. were administered orally. Following such doses the basal metabolic rate increased 20 to 30% in the first hour, and was maintained at this level for about 24 hrs. The normal basal metabolic rate returned on the third day. None of these subjects exhibited signs of nervousness, anxiety, trembling, hunger or palpitation. Following the administration of such daily doses for over 2 months, no changes in the heart rate or temperature were observed. When the dosage was raised to 5 or 10 mg. per kg., the temperature and the heart rate remained normal, but copious sweating developed. Doses above 10 mg. per kg. resulted in an elevation of the temperature of 3° C. The rate of respiration rose 15 to 30 per min. and the heart rate 20 to 30 per min. All the patients lost weight without restriction of diet. The greatest rate of loss of weight was 1.7 kg. per week. The average loss of weight, following a daily dose of 3 mg. per kg., was 0.9 kg. More vigorous doses combined with dietary régime have been purposely avoided. All the patients felt better following the administration of dinitrophenol. No hyperirritability was noted, and this is considered a distinct advantage over thyroid. The authors emphasize that they did not try the drug over a prolonged period, and hence they cannot express opinion on this point. They also urge against the administration of dinitrophenol in patients with diabetes.

In a subsequent report Tainter, Stockton and Cutting<sup>12</sup> describe more fully their experiences with 113 cases of obesity. These patients, mostly women, were not selected cases, and in about one-half of them dinitrophenol was administered only after thyroid and dietary régime had failed. The drug was administered in capsules containing 100 mg. of the sodium salt or its equivalent, 75 mg. of the acid. In this study the dosage was not proportional to the body weight, but it was given in accordance with the desired rate of weight reduction. The treatment usually started with the administration of 1 or 2 capsules with meals, and after the lapse of a week the medication was increased as necessary, until a weight loss of 0.9 to 1.4 kg. (2 to 3 pounds) was produced weekly. If the patient was on a special diet before the administration of dinitrophenol, this was continued; otherwise the patient maintained a normal diet. The average initial weight of the 113 patients was 85.5 kg.

(188 $\frac{2}{3}$  pounds). The average length of treatment was 40 days, but some were treated as long as 125 days. The average loss of weight was 0.7 kg. (1 $\frac{1}{2}$  pounds) per week. The average total loss was 4 kg. (8 $\frac{4}{5}$  pounds). The average dose was 2.9 capsules, corresponding to 1.5 capsules per 45 kg. (100 pounds) of the initial body weight. No general relationship existed statistically between a given dose and the resultant weight loss. While in 7 cases a dose of 1 capsule per day produced the normal loss of weight, in another group of 12 cases, 5 to 6 capsules had to be administered daily. The loss of weight takes place predominantly from the hips and abdomen.

True failure was encountered in 9 patients, in whom unpleasant side reactions such as cystitis, derangement of the taste, gastro-enteritis and skin lesions forced the discontinuance of the treatment. About one-fourth of the entire series of 113 patients complained of perspiration and sensation of warmth. The authors claim that the effect of dinitrophenol differs from that of thyroid. This is supported by the difference in the effects of dinitrophenol and of thyroid on the cholesterol metabolism and on tadpole metamorphosis.

Cutting and Tainter<sup>13</sup> have also reported on the metabolic action of dinitrophenol in man. The effect on the basal metabolic rate, on the nitrogen balance, on urinary organic acids, and on the body weight was studied in subjects on a balanced diet, and on an unbalanced diet with a maximal amount of carbohydrate, fat and protein. The drug was administered by mouth for 7 to 16 days. Although the basal metabolic rate rose from 30 to 50%, the subjects excreted less nitrogen than they ingested, and yet there was a definite loss of body weight. This indicates that the body proteins were probably not broken down. The output of the urinary organic acids was not increased, indicating that the fats were completely burned without giving rise to acidosis. The study indicates that under the effect of dinitrophenol carbohydrates and fats are primarily burned.

Masserman and Goldsmith<sup>14</sup> have studied the problem of whether the drug would be efficacious in increasing the subnormal metabolic rate often found in dull, depressed, listless and apathetic psychopathic patients. In this series the toxicity of the recommended doses seemed to be considerably higher than heretofore reported. The primary warning noxious action manifested itself in a fall of the blood pressure, onset of acidosis, progressive tachycardia and torpor. The evaluation of the psychotherapeutic activity was difficult, because of the possible spontaneous variations. Of 18 patients, 5 showed toxic reactions, in one instance resulting in death. Indeterminate or adverse psychotherapeutic effects were observed in 8 and 4 cases respectively. In 6 cases, improvement was attributed to the medication. The authors point out that dinitrophenol is unpredictably toxic to some patients. Anderson, Reed and Emerson<sup>15</sup> have reported a case with chronic hypertrophic arthritis, in which, after a total of 39.3 mg. per kg. over 14 days, severe intermittent joint pains appeared over areas previously not involved. This was considered as an allergic response to the drug. In discussing the toxicity of dinitrophenol, these authors remark: "In our opinion, it is yet to be demonstrated that this drug is as safe and satisfactory for weight reduction in human beings as other methods in common use." Geiger<sup>16</sup> reports the death from dinitrophenol of a physician

who took a very large dose, apparently with suicidal intent. Four hours after ingestion of the drug he became apprehensive, restless and uneasy. He felt warm and perspired freely. There was a sensation of air hunger, without dyspnea. The temperature rose to above 110° F., and following death there soon developed an intense rigor. It was estimated that the patient took a dose of 2.5 to 5 gm.—which is about 15 times the therapeutic dose.

While final judgment cannot be expressed as yet on the therapeutic value of dinitrophenol, the above analysis of the literature indicates that it is a substance which well deserves further trials in therapy. Its administration under medical supervision in doses advocated is apparently safe. Studies on its prolonged usage are still lacking.

S. W.

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#### RADIOLOGY

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#### MALACIC DISEASES OF BONE.

PRESENT-DAY interest in this subject was focused in a symposium conducted at the annual meeting of the American Roentgen Ray Society in September, 1932.

Dresser<sup>1</sup> distinguished osteitis fibrosa cystica unassociated with an endocrine disturbance from that which is a manifestation of a systemic disease caused by overactivity of the parathyroid glands. He dealt

particularly with the latter, however. MacCallum<sup>2</sup> first showed that hypofunction of the parathyroid glands resulted in tetany, the symptoms of which could be relieved by administration of calcium. The fact that these glands exercise a control over calcium metabolism was thus established. Mandl<sup>3</sup> definitely established the relation of parathyroid dysfunction to osteitis fibrosa cystica by removal of a parathyroid adenoma.

Increase in the calcium content of the blood, lowering of the blood phosphorus, increased elimination of calcium and phosphorus by the kidneys, and decalcification of the bones result from overactivity of the parathyroid glands. The disease may occur at any age, in either sex, but it most commonly affects women between 30 and 60 years of age. Most patients complain, first, of pains in bones and joints. In the advanced stages, skeletal deformities may develop as the result of softening, bending, and fractures of the bones. Gastro-intestinal symptoms are not uncommon: loss of appetite, nausea and occasionally vomiting. There are usually slow, progressive loss of weight, and secondary anemia. There may be a palpable tumor in the neck (parathyroid adenoma). The urinary symptoms are important. Renal function is impaired. Polyuria is frequently present and the urine is of low specific gravity and contains albumin and casts. The increased output of calcium and phosphorus leads to the formation of urinary calculi, which may be bilateral. Any abnormal rarefaction of one or more bones of a patient who presents renal calculus should be regarded as ground for suspecting osteitis fibrosa cystica. A correct determination of the blood calcium and phosphorus is essential to the diagnosis. The concentration of serum calcium is elevated (more than 10 mg. per 100 cc.) and the serum inorganic phosphorus is low (less than 4 mg. per 100 cc.). The parathyroid tumors which have been described, vary in size from a few mm. to 5 or 6 cm. in diameter. The microscopic picture is that of an adenoma which may be difficult to distinguish from normal parathyroid tissue. Abnormal deposits of calcium in the soft tissues have been described. The roentgenologic findings are: (1) Generalized decalcification of bone together with localized regions of increased density of bone; (2) generalized or localized formation of cysts. Generalized osteoporosis may be seen without formation of cysts, and conversely, formation of cysts may occur without appreciable osteoporosis. The bones of the skull present mottling of the vault which is the result of small, irregular areas of condensation of bone alternating with areas of rarefaction. In advanced stages of the disease the cranial bones may become much thickened. The upper and lower jaws are both favorite sites for formation of cysts. The teeth are often carious and abscessed. There may be abnormal curvatures of the spinal column, which become more pronounced as the disease progresses. The vertebral bodies are narrowed, the bony texture is altered, and the articular surfaces have a tendency toward concavity. The intervertebral spaces are not narrowed and the vertebral processes do not appear abnormal. The pelvis is frequently the site of very extensive cystic changes, and abnormalities of contour develop as the weakened bones give way to the body weight. The ribs are fairly regularly involved in the cystic process, and late in the disease the thorax may cave in with serious cardiac and respiratory embarrassment.



Cysts occur in all the long bones and in the bones of the hands and feet. The bones may become expanded and the cysts trabeculated, producing the appearance of a giant-cell tumor, or there may be localized areas in which bone trabeculae are completely lost, but without expansion or other alteration in the contour of the bone. Fractures of the extremities are common and seem to heal readily, but without excess of callus. A cyst which has been the site of spontaneous fracture or surgical interference often will regress rapidly. Too sharp a distinction should not be drawn between localized and generalized osteitis fibrosa cystica.

Ballin<sup>4</sup> stated that if a parathyroid gland were irritated by hyperplasia or by an adenoma, its function would be stimulated and, as a result, more parathormone would get into the circulation. This increased parathormone leads to decalcification of the skeleton, through increase in the calcium content of the blood serum; the calcium is derived from the great calcium storehouse, the skeleton. In addition to the train of symptoms described by Dresser, Ballin stated that hyperealecemia leads to lessening of the muscle tonus and to secondary deposits of calcium in certain places where infection or other conditions may cause roughening and thus make an especially inviting location. Microscopic examination also reveals widespread deposits of calcium in the liver, spleen, intestinal mucosa and kidneys. Ballin stressed these latter in the consideration of certain cases in which Oppel claimed arthritis resulted from parathyroidism. If hyperealecemia exists, secondary deposits of calcium will lead to ankylosis in cases of otherwise non-ankylosing arthritis and, therefore, parathyroidectomy will prevent and even cure some of these beginning cases. To diagnose them, evidences of other disturbances of parathyroid function, such as hypercalcemia or severe muscle hypotonia are necessary. Cases of parathyroidism without demonstrable involvement of bone have occurred. Absence of hyperealecemia and other chemical data should not invalidate the diagnosis of parathyroidism if clinical and Roentgen findings and hypotonia, for example, favor the diagnosis.

Morse,<sup>5</sup> continuing the survey of malacic diseases of bone, in a first group placed those diseases in which the primary defect is in the mesoblast. The mesoblastic tissue as a whole, all over the body, is probably defective and, as a result, the ability of the osteoblastic cells to lay down the connective-tissue groundwork for bone is lacking. The bones are fragile not because there is any primary defect in calcium metabolism, but because the connective tissues are unable to build up a groundwork on which enough lime may be deposited. In this class come osteogenesis imperfecta and fragilitas ossium, probably the same disease; the first the fetal or infantile manifestation, and the second an adult form. These diseases have a particular tendency to be hereditary and familial, to be characterized by multiple fractures which heal normally, to give evidence of their presence by the characteristic blue sclera of those affected, and also to show various evidences of multiglandular endocrine disturbances of more or less indefinite form. The blood calcium and phosphorus levels are usually normal. In the second group he placed those diseases which are due to a primary defect in absorption and fixation of lime; either the intake of calcium is deficient in general, or is insufficient to meet an unusual physiologic demand, or the intake of vitamin D is deficient or all of these factors combined

have an effect. Rickets and osteomalacia proper are in this class; rickets is the infantile, and osteomalacia the adult type of the same disease. Here there is no mesoblastic defect; there is no deficiency of connective tissue, and no lack of capacity on the part of the bone-forming cells to lay down sufficient groundwork for lime to be deposited on, but the dyscrasia is one having to do with the inability to fix lime in the new forming bone or with inability to obtain enough lime for this purpose. In these cases there is usually no elevation in the levels of blood calcium. The levels of phosphorus are also usually normal, except in those atypical forms of rickets known as high-phosphorus rickets which probably have other relationships. Secondary hyperplasia of the parathyroid gland is the rule, but ordinarily rickets and osteomalacia are not primarily parathyroid in origin and not ordinarily amenable to surgical treatment. In cases of a third group, the general characteristic is increased excretion of lime in the urine, a sort of leakage of lime, due possibly to various causes but associated with various diseases of other endocrine glands. The malacia involving bone in severe cases of exophthalmic goiter, that in pancreatic diabetes with marked sclerosis of the pancreas (possibly related to a chronic acidosis), the decalcification of bone in some cases of basophil adenoma of the pituitary body, and certain cases of suprarenal tumor, make up this group. Renal rickets presents a most striking form of malacia of bone; the primary defect probably is retention of phosphorus. The result of this retention of phosphorus is marked responsive hyperplasia of the parathyroid gland, undoubtedly brought about in an effort to lower the level of blood phosphorus; its secondary result is to increase the concentration of blood calcium, to draw on the reserve of lime in the skeleton, and diffusely to decalcify the bones. Removal of the parathyroid gland, or any other therapeutic measure undertaken with the idea of alleviating the affection is not to be considered. In a group that must be distinguished from others, Morse placed those diseases in which defects in bone are produced by pressure erosion: Hand-Schüller-Christian's disease, Gaucher's disease, Niemann-Pick's disease and Hodgkin's disease. The roentgenologist often finds it difficult to separate members of this group from various others which truly belong in the classification of malacia. Generalized carcinomatosis might also be placed in the same category. In a single group, as caused either by primary parathyroidism, or at least by overactivity of the parathyroid gland brought on by some special cause, Morse placed osteitis fibrosa, osteitis deformans (Paget's disease), leontiasis ossium, the ankylosing polyarthritis of Oppel, multiple and possibly single giant-cell tumor and multiple myeloma of the plasma-cell type. The evidence at present seems to him to point to the fact that operation and removal of some of the parathyroid glands lead, in most cases, either to complete clinical cure or at least to marked clinical benefit. He considered myeloma to be a primary osteoblastic tumor arising from the primitive osteoblasts and at present a malignant manifestation or a malignant end-stage of osteitis fibrosa cystica.

Bromer<sup>6</sup> regarded fetal rickets as a definitely established clinical entity. Infantile rickets may be seen in two types: the passive type is seen in severe cases, and the infant, because of muscular weakness, does not move the extremities; the active type affects children who are

of a good state of nutrition and bodily activity, in spite of the rickets. Bromer distinguished three stages seen roentgenographically, covering the progress of the disease from the first roentgenologic signs to complete healing.

Hodges and Ledoux<sup>7</sup> affirmed that osteomalacia is the rickets of adults and quoted McCrudden's careful work and his interpretation of microscopic and chemical studies as showing that the physiologic destruction of old bone and its replacement by new osteoid tissue went forward in a normal fashion, but that for some reason the calcium liberated from the old bone was not utilized by the organism to calcify the new osteoid tissue, but instead was lost from the body, principally in the feces. The treatment of osteomalacia is the treatment of rickets: a diet adequate in all respects, particularly in vitamin D, plus an adequate amount of sunshine.

Peirce<sup>8</sup> did not feel that evidence is sufficient at present to justify placing giant-cell tumor in the group of "primary parathyroid osteomalacias." Hall<sup>9</sup> suggested that the toxins from the same infectious process that plays a major part in the etiology of spondylitis act as parathyroid stimulants, so that parathyroidism becomes the most important, if not the primary, factor in producing the para-articular changes. As to whether there may not be a hereditary or familial tendency to parathyroid dysfunction to explain the quite generally accepted hereditary factor in spinal ankylosis of the Bechterew type is a problem worthy of careful study. Osteopoikilosis, according to Wilcox,<sup>10</sup> is characterized by a disseminated condensation of the bones of the skeleton, without clinical symptoms. All of the bones have been shown to be involved, except the bones of the skull. Three types have been described: the spotted form, which is the one most commonly seen; the striated form, which is relatively rare and in which there are long, narrow striations of dense bone, and the mixed form, which is a combination of the two. It is a hereditary anomaly developing from a congenital anlage. Neither osteopoikilosis nor marble bone, in the opinion of Pirie<sup>11</sup> offers any suggestion of being related to the parathyroid gland.

Vogt<sup>12</sup> pointed out that renal rickets is a term used to denote rachitic changes in bone sometimes associated with chronic nephritis in children. It is not a primary entity, but a manifestation of disturbed mineral metabolism resulting from renal disease. Rickets, as seen in infants, is a deficiency disease, that is, certain vital factors essential to anabolism of bone are lacking. Vitamin D acts as a regulator of calcium and phosphorus metabolism and permits the organism to operate with greatly increased economy with respect to these minerals. The concentration of calcium and inorganic phosphorus in the serum is determined by at least four factors; namely, the calcium content of the diet, its total phosphorus, the ratio of these components in the diet, and the amount of vitamin D preformed or produced by radiation. Without the balancing effect of vitamin D, calcium and phosphorus in the serum vary directly with concentration of the same elements in the diet. Furthermore, there seems to be antagonism between calcium and inorganic phosphorus. A high concentration of one element depresses the concentration of the other *component in the serum*. The primary factor responsible for the bony changes of rickets is an imbalance or deficiency

of calcium and phosphorus in the blood. The pathognomonic histologic lesion is due to defective mineralization of growing bone. Renal disease is recognized as one of the factors in alteration of the levels of the inorganic constituents of the blood. Therefore, in certain types of nephritis, conditions are present which are favorable for the development of rickets. Roentgenologic findings vary in different cases, and sometimes in the same case at different times. Skeletal development is always retarded, and disturbances of growth are often manifested by the presence of transverse striæ near the ends of long bones. The lesions may be asymmetrical, or different bones may be unequally involved. Roentgenograms of the skull show fine, granular mottling and generalized osteoporosis. There is irregular mottling of the anterior ends of the ribs and defective subperiosteal calcification along the lateral margins. The ends of the diaphyses are identical in appearance with that produced by ordinary rickets. Defective subperiosteal calcification is seen at the upper ends of the tibiæ, medially; the metaphyses are smooth and dense. Osteogenesis imperfecta is a deficiency of osteoblasts, resulting in deficient ossification of bone, this being productive of numerous and repeated fractures. On chemical analysis there is no lack of the inorganic constituents of bone, and fragility therefore cannot be dependent on this factor. Bromer<sup>13</sup> found but one reference to an actual pathologic finding in the parathyroid bodies in such a case. This was a case of bone dysplasia and unusual vascularity of the parathyroid glands, with a relatively small amount of parenchymal tissue. In an appended note he tabulated 3 other cases in which, histologically, there was hyperplasia of the parathyroid glands.

Golden and Abbott<sup>14</sup> concluded that hyperthyroidism produces an abnormal elimination of calcium, the mechanism of which is not understood. It seems to be frequently associated with decalcification of the bones demonstrable in the roentgenogram by suitable comparison with the normal; the decalcification is so slight as to be of little if any importance. In rare cases the decalcification of the bones may be extreme. Its appearance, however, is not characteristic of thyrotoxicosis. In cretinism and infantile myxedema there is widening of the cortex of the long bones, without loss of calcium. Hypothyroidism in adults apparently is associated with no greater incidence of decalcification of bones than that which might be encountered in any group of patients of the same age. Although suprarenal secretion either directly or indirectly influences calcium metabolism, and although the suprarenal glands may be indirectly involved in a pluriglandular imbalance in certain cases of osteomalacia, the evidence does not seem to justify the assumption that decalcification of the bones results directly from suprarenal disease or dysfunction. The available evidence indicates that loss of calcium may take place in diabetes, especially with acidosis. The question is how much of this is of endocrine and how much of nutritional origin. Roentgenologic evidence of definite important skeletal decalcification in diabetic adults is lacking.

Hand-Schüller-Christian's disease, according to Rowland,<sup>15</sup> is a rare, probably familial, constitutional disorder of metabolism in which a deposition of lipid mixtures, particularly cholesterol and its ester, takes place, leading to a characteristic hyperplastic reaction in the reticular endothelial or the histiocytic apparatus. The common patho-

logic change is a granuloma-like accumulation arising from connective tissue in many parts of the body. Usually three cardinal symptoms, bony defects, exophthalmos and diabetes insipidus, are present but it should be understood that no one of these is essential and that there are others which are sometimes of equal importance. The resorption of bone resembles that of osteomalacia in many respects; that is, atrophy with demineralization, although it is really atrophy of bone from pressure. The membranous and flat bones are most often involved, but changes may occur in any part of the skeleton. Roentgenographically, changes in the superior and inferior maxillæ, flat bones of the pelvis, scapulæ, ribs, vertebræ and the long and short bones have been observed. When there has been involvement of the pituitary gland, destructive changes in the sella and Roentgen evidences of tumor have been noted. The endocrine disturbance seems to be the result of the lipoidosis.

Erythroblastic anemia (Cooley's syndrome) has been thoroughly reviewed by Baty and others.<sup>16</sup> Borzell<sup>17</sup> has compiled the characteristic roentgenographic findings as striations in the calvarium with trabeculation of the facial bones, clavicles, scapulæ, and long bones with expansion of the shaft and thinning of the cortex in the latter. The changes in sickle-cell anemia are similar in some respects to those found in erythroblastic anemia, but not by any means as profound. With any improvement under radiotherapy there appeared a greater tendency to transverse striation, particularly at the metaphyses, together with definitely increased density of the metaphyses. In the rapidly accumulating literature on this subject one finds criticism of some of the assertions made in the foregoing articles. Bauer<sup>18</sup> stressed the point that all cases thus far reported have been due to parathyroid adenoma. The serum calcium in these has been permanently elevated.

Nachlas<sup>19</sup> studied the serum calcium in 37 cases of arthritis and found no change from normal. In the same patients the blood phosphorus was studied with the idea of distinguishing hypertrophic from infectious arthritis, but no uniform variation from the normal reading was obtained. Compere<sup>20</sup> confirmed the opinion that the only definite test of parathyroid hyperfunction which is acceptable is the study of calcium metabolism and the demonstration of a negative calcium balance. The balance is consistently negative; the serum calcium is high; the plasma phosphates are low, and true adenomas of one or more of the parathyroid glands are found in nearly all cases at operation or postmortem examination.

A. M.  
C. G. S.

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## PHYSIOLOGY

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SESSION OF MARCH 19, 1934

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**The Effect of Removal of the Adrenal Glands Upon Pancreatic Diabetes in the Cat.** C. N. H. LONG and F. D. W. LUKENS (George S. Cox Medical Research Institute, University of Pennsylvania). In the past numerous attempts have been made to show that the adrenals play some part in the chain of events that follows pancreatectomy, but the most authoritative workers have concluded that no such interrelationship exists. However, in recent years it has been abundantly demonstrated that hypophysectomy, either before or after removal of the pancreas, greatly ameliorates the subsequent course of the diabetes. The final pertinent fact that led us to attempt another investigation of the relation of the adrenals to pancreatic diabetes in certain animals is that hypophysectomy causes a marked atrophy of the adrenal cortex and might be producing its effects through these glands.

In 5 cats we have removed, in stages, all the pancreas and both adrenal glands. The periods of survival were 12, 11, 8 and 6 days, while another animal was sacrificed in good health on the 7th day for liver glycogen determination (2.5 gm. %). One of the animals was diabetic at the time the second adrenal was removed. Its subsequent behavior was no different from the others.

None of the animals presented the usual clinical picture of those depancreatized with the adrenals present. They remained active and ate fairly well up to the day of death. They have all died suddenly in convulsions in marked contrast to the ordinary diabetic cats, which gradually sink into coma. A commercial preparation of adrenal cortical extract was injected daily, but not insulin. Although supposedly adequate amounts of cortical hormone were given, the animals resembled in some respects those suffering from adrenal insufficiency.

The most striking findings have been (a) the fasting (overnight) blood sugars in the majority of observations were not above normal and showed a remarkable tendency after the first few days to fall to such low levels that convulsions, relieved by glucose, have supervened. (b) The daily glycosuria was very mild or absent, depending upon the

amount and type of diet. When glycosuria was present the  $\frac{D}{N}$  ratios were not those of pancreatic diabetes. (c) Metabolic balance sheets reveal that large quantities of the glucose of the diet were utilized but the tolerance was not normal. (d) The feeding of glucose by stomach tube or its intraperitoneal injection gave variable results. The animals showed a practically normal tolerance at some times, while at others it was decreased.

In 7 animals similar experiments were carried out but one adrenal was left intact; 3 of these were not treated with insulin and died of a rapidly progressing and typical diabetes in 5 days or less. The remainder were treated with insulin. Three showed no diminution in their insulin requirement on a standard diet. The remaining animal had an increased sensitivity to insulin for the first week after the last of the pancreatic tissue was removed. Following this the usual amounts of insulin were required.

While this work was in progress there appeared a paper by BARNES, SCOTT, FERRILL and ROGOFF (*Proc. Soc. Exp. Biol. and Med.*, 51, 524, 1934). These workers report that if unilateral adrenalectomy is performed on dogs prior to total pancreatectomy, the course of the ensuing diabetes is very mild. Furthermore, unilateral adrenalectomy, after total pancreatectomy either enables the animal to exist on greatly reduced amounts of insulin or to live for a long time without any.

At the present time we have 1 dog in which unilateral adrenalectomy was performed before total pancreatectomy. It appears to differ from the cats with these operations but it is too soon to draw any conclusions. The possibility of a species difference is considered.

Our conclusions are that total adrenalectomy in the cat greatly ameliorates the diabetes following pancreatectomy. In this species, unilateral adrenalectomy does not produce any change.

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**Further Studies on the Effect of Amebicidal Drugs on Tissue Culture Cells.** MARY JANE HOGUE (Anatomical Laboratory, University of Pennsylvania). Tissue cultures were made from the intestines of 8-day-old chick embryos. Locke-Lewis medium was used. The drugs used were arsenious trithio-salicylic acid, carbarsone, kurchi bismuth iodid, proparsamid, and vioform. These were added to Locke-Lewis media in the dilutions 1 to 1000, 1 to 10,000 and 1 to 50,000. The effect of the various dilutions on the tissue culture cells was studied. Arsenious trithio-salicylic acid in all the dilutions was injurious to the tissue culture cells. Carbarsone, diluted 1 to 1000, when it was left on the culture 24 hrs., affected the epithelial cells but not the other cells. In higher dilutions it did not affect any cells. Kurchi bismuth iodid was injurious to all the cells in dilution 1 to 1000. In dilution 1 to 10,000 it did not affect the epithelium but killed or injured the fibroblasts. In dilution 1 to 50,000 the tissue culture cells grew fairly well. Proparsamid in its lower dilutions was injurious to the nerves and slightly injurious to the epithelium. It did not affect the fibroblasts when used for only 24 hrs. Vioform is only slightly soluble in Locke-Lewis solution. The tissue culture cells did not phagocytose it. It was more injurious to the fibroblasts than to the epithelial cells but it affected all the tissues in all the dilutions used.

**An Adaptation of the Transparent Chamber Technique to the Skin of the Body.** ROY G. WILLIAMS (Anatomical Laboratory, University of Pennsylvania). A skin flap was made in the long axis of a rabbit's body in such a manner that its original bloodvessels and part of its nerves were preserved. This flap was sufficiently long to allow the installation of a transparent chamber and to permit unimpeded observation of the chamber under the microscope. Eight such flaps have been made and chambers installed in 6. Vessels appeared on the table in all cases and grew entirely across in 1. The new tissues from the flap invade the chamber in much the same manner as they do when the chamber is placed in the ear. Such an installation provides an opportunity for comparing the behavior and growth of the tissues in the ear with that in another part of the animal's body.

When the chamber in the flap is provided with a removable top so that direct access to the growth may be had, an opportunity is afforded for implantation of other tissues into the chamber or for direct manipulation of the chamber contents. The exposure of the growing region by removing the top and then replacing it has been done successfully in several cases. A modified chamber designed for this purpose will be described elsewhere.

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**The Nussbaum Experiment on Renal Secretion.** RUDOLF T. KEMPTON (Laboratory of Pharmacology, University of Pennsylvania). When ligation of the renal arteries in American frogs is performed exactly in the manner of the original Nussbaum experiment, urine continues to be excreted after injections of urea. Direct observation of the kidneys of such animals during life showed that the intention of the experiment, complete abolition of glomerular function, had not been realized. Active circulation was observed to persist in the posterior part of the kidneys. Despite ligation of all renal arteries, blood reached the areas supplied by the most posterior of the renal arteries through anastomoses with the distribution of the rectovesical arteries or with the renal portal vein. The volume of this collateral circulation was greatly increased by injections of urea. When this circulation was suppressed by additional ligatures no urine could be obtained from the bladder even after urea injections.

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**Micro Determination of the pH Fluid in Renal Glomeruli and Tubules.** HUGH MONTGOMERY and J. A. PIERCE (Laboratory of Pharmacology, University of Pennsylvania). By administering phenol red subcutaneously or intravenously the colorimetric method of estimation of pH has been adapted for use on 0.2 mm. of glomerular fluid or tubular fluid. The average error on known solutions is pH 0.03. The method is applicable to plasma when precautions are taken to prevent metabolism of the red cells, and when a constant correction factor is applied.

In the frog the identity of pH of glomerular fluid and plasma was established.

A quinhydrone electrode has been devised for estimation of the pH of 0.02 mm. of fluid. The average error on known solutions is pH 0.03.

Results by both methods show that the pH of glomerular fluid, of proximal tubular fluid, and of intermediate tubular fluid in *Necturus* is the same as that of the plasma, and that the decrease in pH takes



place in the distal tubule. The pH of distal tubular fluid was in no case as high as that of the corresponding glomerular fluid, or as low as that of the corresponding urine. No constant relationship between distance down the distal tubule and per cent decrease in pH was demonstrated.

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**The Sympathetic Control of the Heart.** D. W. BRONK, L. K. FERGUSON and D. Y. SOLANDT (Johnson Foundation for Medical Physics, University of Pennsylvania). In order to investigate the activity of the sympathetic motor nerve cells which have an accelerator influence on the heart, and to study the reflex control of this mechanism, we have recorded by means of a vacuum-tube amplifier and oscillograph the efferent impulses in small nerve twigs running from the stellate ganglion to the heart in cats. Normally there is a continuous discharge of impulses which thus provide a constant accelerator influence on the heart. Under certain conditions the impulses are grouped into waves which are synchronous with the pulse and under certain other conditions nervous activity is completely inhibited with each inspiration. Such variations indicate the striking fluctuations which take place in the activity of the sympathetic centers under the influence of various factors, such as the activity of adjoining centers, degree of respiration, nature of the afferent control, and so forth.

As a general rule any rise in mean blood pressure is associated with a decrease or complete inhibition of the sympathetic discharge. This is to a very considerable extent accomplished by way of the afferent impulses going over the carotid sinus and aortic nerves. Distension of a carotid sinus or electrical stimulation of a carotid sinus nerve produces inhibition of the sympathetic efferent discharge for a period which increases with an increase in the degree of afferent stimulation. This reflex is bilateral and simultaneous stimulation of two carotid sinuses produces a summation of inhibitory effect.

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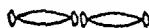
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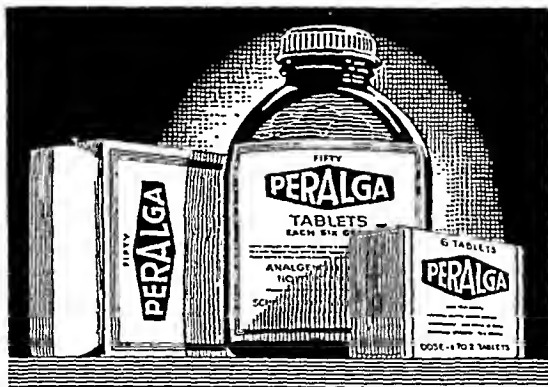
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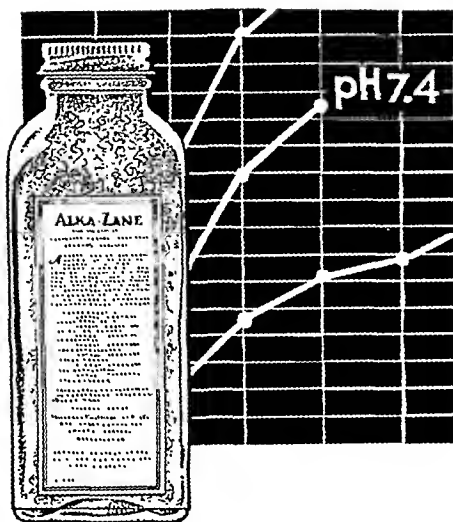
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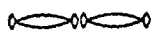
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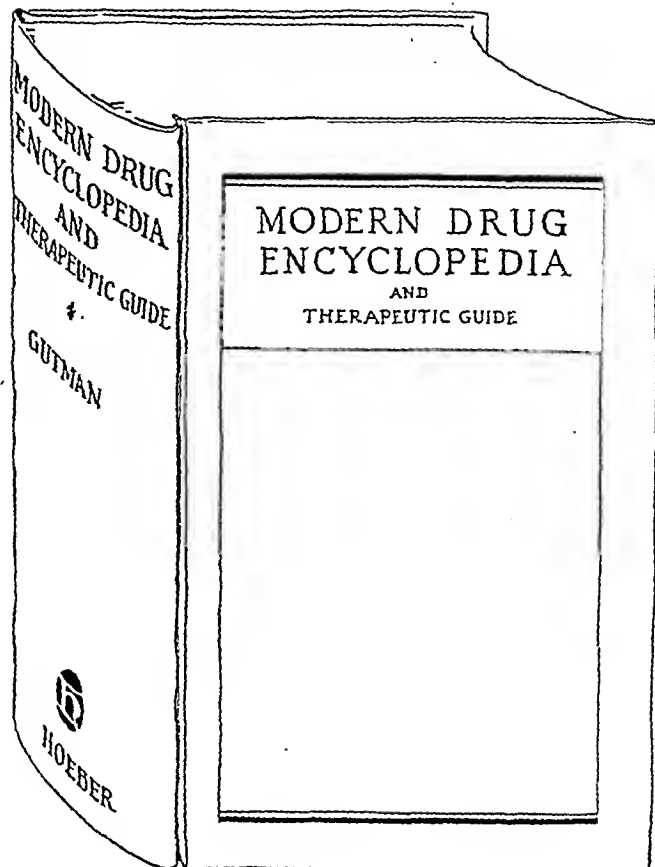
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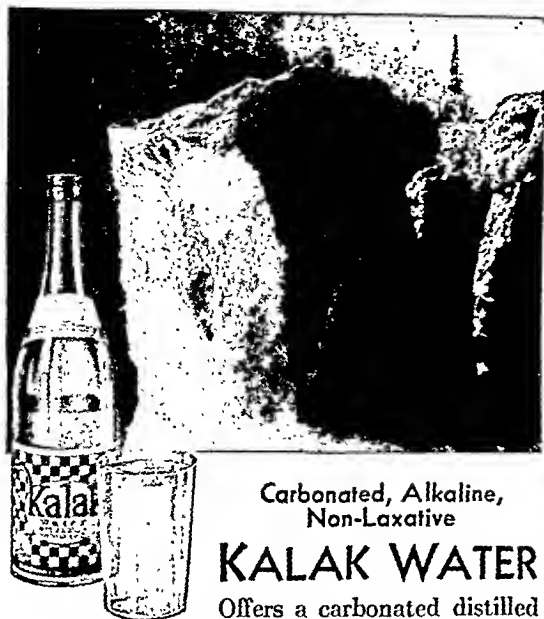
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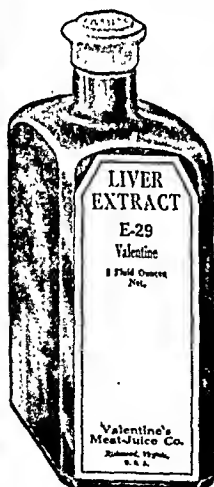
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<sup>1</sup> Science, 73, 243 (1931)

<sup>2</sup> Jour. Nutrition, 6, 179 (1933)

<sup>3</sup> Klin. Wochschr., 12, 1241 (1933)

<sup>4</sup> Science News Letter, p. 31, Jan. 13 (1934)

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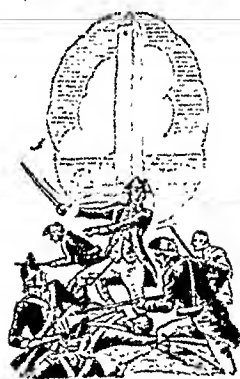
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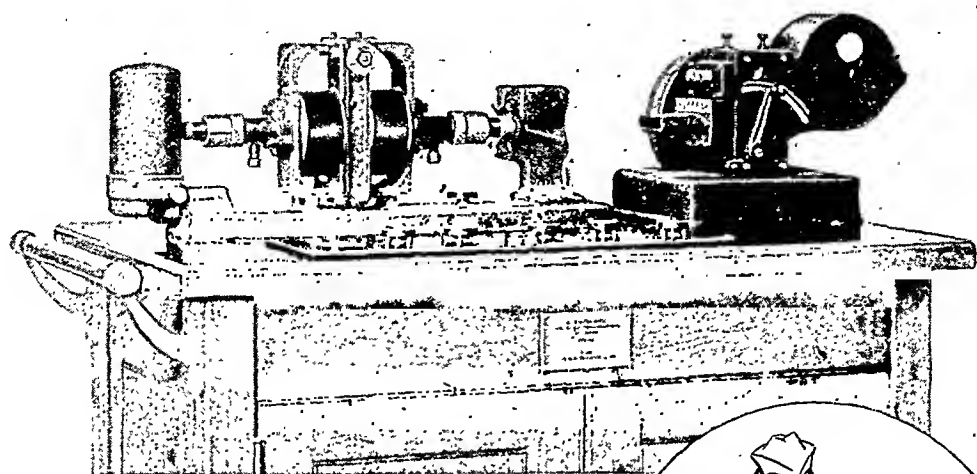


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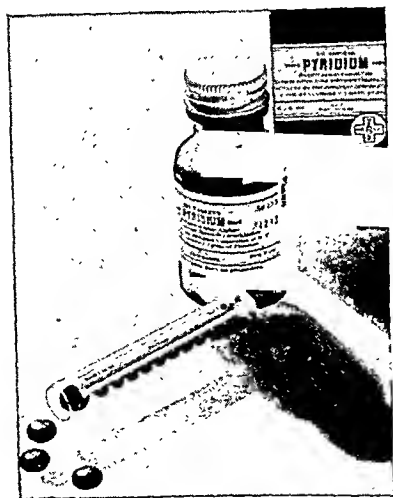


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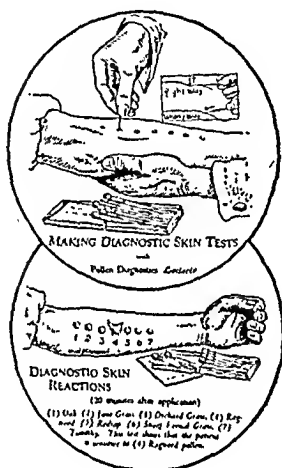
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THE  
AMERICAN JOURNAL  
OF THE MEDICAL SCIENCES

JUNE, 1934.

ORIGINAL ARTICLES.

THE MEDICAL TREATMENT OF THE THYROCARDIAC.\*

BY CARY EGGLESTON,

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NEW YORK.

THE Graduate Fortnight of the New York Academy of Medicine, so recently terminated, has dealt rather extensively with hyperthyroidism, hence I need not burden you with a repetition of the general clinical picture of the thyrotoxic state. Nor does there seem to be need to discuss in detail the diagnosis of thyrotoxicosis or the clinical differentiation between the hyperthyroidism of Graves' disease and that present in toxic nodular goiter, if, indeed, there be any. The factor of first importance in the thyrocardiac is the presence of thyrotoxicosis, and this is common to both clinical forms of the disease. What is meant by the term "Thyrocardiac?" Perhaps as satisfactory a definition as any is: The thyrocardiac patient is one who presents the combination of hyperthyroidism with evidences of cardiac failure, either congestive or anginal, with or without evidence of structural lesions in the heart or arteries.

The incidence of thyrocardiac trouble as determined statistically varies widely in different parts of the world, in different clinics in the same country, in the different age groups and somewhat according to whether one is dealing with Graves' disease or with the toxic form of nodular goiter. It is probably both useless and misleading, therefore, to attempt any numerical statement of incidence but it may safely be said that the condition is decidedly commoner than is generally recognized.

That the structurally normal heart is subjected to overwork in hyperthyroidism is evidenced by the almost constant tachycardia

\* Read before the joint meeting of the sections of Surgery and Medicine at the New York Academy of Medicine, New York City, December 1, 1932.

which persists with little diminution during sleep. It is even present in the isolated, perfused heart from the animal poisoned by thyroxin or thyroid extract and has been observed in surviving, isolated segments of such poisoned hearts. It is therefore due, in part at least, to a direct poisoning of the heart muscle itself. Such a poisoned heart has been shown, also, to exhibit increased oxygen consumption, an increased lactic acid production and a hypersensitivity to relative oxygen want; all of which indicate the presence of a fundamental change causing increased rate of myocardial metabolism.

Despite the evidence of pronounced poisoning of the myocardium, postmortem studies fail to show any constant structural changes other than hypertrophy. Occasional instances of toxic inflammatory myocarditis have been found without other discoverable cause than the thyroid intoxication. The common absence of structural change is quite in harmony with the clinical observation that ablation of the thyroid gland is often followed by prompt and lasting disappearance of all evidences of heart impairment in cases previously suffering from marked congestive failure and auricular fibrillation. Finally structural changes are not found in the hearts of animals poisoned by thyroid or thyroxin. It is evident that the toxic effects upon the heart are for the most part functional and reversible.

In view of the elevated general basal metabolism of hyperthyroidism, it is not surprising to find such other common manifestations of cardiac overwork as: hypertrophy of the heart; visible and palpable cardiac overactivity; increased blood pressure; dyspnea on mild exertion; and marked fatigability. Furthermore, disturbances of rhythm are frequent, especially auricular fibrillation and sometimes flutter, less often heart-block and extrasystoles. All of these are probably due to direct cardiac intoxication and heightened sympathetic activity. When present, they impose an added load upon the heart and systemic circulation.

It is not, therefore, a cause of wonder that cardiac failure sometimes complicates hyperthyroidism in patients otherwise free from cardiac or vascular disease. It is remarkable rather under such circumstances that failure of the otherwise sound heart is relatively uncommon. The majority of patients classifiable as thyrocardiac are found among those in whom there are present both hyperthyroidism and structural cardiac or vascular disease. In these the load imposed by the thyrotoxicosis is the factor primarily responsible for the development of the manifestations of cardiac failure.

Four clinical groups of thyrocardiac patients may be distinguished: First are those under 40 in whom the cardiac failure is apparently due entirely to the toxic effects of Graves' disease. The diagnosis of Graves' disease is usually evident from its well developed symptoms. Cardiac failure is of the congestive type and is rarely very pronounced. The cardiac overaction with its attendant tachycardia, sharp and accentuated apical first sound, apical systolic murmur, accentuated pulmonic second sound, the occasional accentuation

of the third heart sound, frequent auricular fibrillation, and evidences of pulmonary congestion may lead to the suspicion that mitral stenosis is present. It is not always possible to be sure whether or not it is present as a complicating factor in a given case. It is likely that the phenomena are merely due to a greatly over-acting, structurally intact heart if they have developed more or less simultaneously with the symptoms of the hyperthyroidism and if close investigation of the patient's past history fails to reveal frequent tonsillitis, chorea, or evidences of rheumatism. The disappearance of the phenomena with the removal of the thyrotoxicosis gives the final answer.

The second group differs from the first only in the knowledge of a pre-existing rheumatic cardiac damage. This group is usually recognized easily by the history and is confirmed by the rather poor response to the usual régime of treatment of the rheumatic cardiac, especially to the use of digitalis.

The third group comprises patients of more than 45 in whom the cardiac phenomena may be due in part to syphilitic, hypertensive or arteriosclerotic changes in the heart. While such structural cardiac changes are often contributory, the cardiac failure is generally precipitated and often maintained by the thyrotoxic state. The underlying cardiac damage may or may not be recognized. The heart failure in this group is usually of the congestive type, though the picture may be that of angina pectoris.

Finally, the fourth group is that of "Masked hyperthyroidism." Here the patients are generally also over 45 and show clinical signs and symptoms predominantly cardiac. Those of hyperthyroidism may be almost wholly wanting. Suspicion of thyrotoxicosis is often raised because of poor response to cardiac therapy, because of the disproportion between the degree of heart failure and the manifest evidences of organic cardiovascular disease, or by both. Diagnosis is established by determinations of the basal metabolism, which, however, may be but slightly elevated; by the findings of slight signs of hyperthyroidism and nodules in the thyroid; or by a therapeutic test with iodine controlled by repeated measurements of the metabolism.

Graves' disease, as mentioned, is the common thyroid disturbance in the first two groups while either Graves' or the toxic form of adenoma may be present in the latter two. Toxic adenoma is probably the commoner in the fourth group.

Differentiation of these groups, while generally possible, is of relatively minor importance so far as immediate treatment is concerned. Their recognition does, however, alter the prospect of later treatment and is of material significance in the matter of ultimate prognosis, especially as to the probability of recurrence of heart failure.

The treatment of the thyrocardiac patient presents two problems: 1. The cardiac failure. 2. The hyperthyroidism. It is a

mistake, however, even where organic heart disease is present in marked degree, to lose sight of the all-important hyperthyroidism. Experience has amply proved that relatively little and sometimes no satisfactory restoration of the heart can be secured so long as the thyrotoxicosis exists. The administration of digitalis rarely controls the heart failure adequately in thyrocardiac patients exhibiting a regular sinus rhythm and is scarcely more effective in those whose hearts show auricular fibrillation. The thyroid toxins seem to be altogether too potent to have their cardiac actions significantly offset by even so powerful a cardiac drug as digitalis. Quinidin will restore the sinus rhythm in many of these patients, but usually the cardiac failure will still persist. This is not to say that these agents are of no value in the care of the thyrocardiac. They often are of help, but the benefits derived from their use are relatively slight and restoration of full cardiac efficiency is seldom attained by their use alone. Treatment must always be directed toward the control of the hyperthyroidism, the cardiac phenomena being dealt with as complications which may or may not be eliminated by control of the thyrotoxicosis.

There are two schools of thought concerning the treatment of hyperthyroidism—the medical and the surgical. My personal leanings used to be toward the medical a number of years ago, especially for the thyrocardiac patient who too often succumbed promptly to operative manipulations on and about his thyroid gland. Medical treatment, if adequately and painstakingly conducted over a sufficiently long period, was capable of curing some cases of Graves' disease and of restoring many others to a reasonable state of health. But at best the results were problematic and failure was the rule in the thyrocardiac case, death merely being deferred for months of progressively increasing invalidism. The results in the thyrocardiac with toxic adenoma were still less promising under medical management. The patient in whom the clinical picture was predominantly cardiac, that is the patient with masked hyperthyroidism, offered an almost hopeless prognosis, probably because the presence of thyrotoxicosis was seldom recognized.

Within the past 10 years, and even more within the past few, both our knowledge of hyperthyroidism and of its combined medical and surgical treatment and our ability to recognize and to treat the thyrocardiac have been advanced enormously by the joint labors of internists and surgeons. Today the proper admixture of medical and surgical therapy makes the results of treatment of the thyrocardiac often so brilliant as to be among our most dramatic therapeutic accomplishments. The outstanding fact today is that these patients can and must be relieved of their thyrotoxicosis through subtotal thyroidectomy. I believe that surgery is an essential step in their successful care and that the prognosis has been changed from generally very bad to generally very favorable, and often to most excellent. This reversal of outlook depends upon the fulfil-

ment of two, and sometimes three groups of requirements. Two of these are medical and one surgical. I shall leave the latter to Dr. Parsons, reserving the privilege of emphasizing a few points that are at least as much medical as surgical. The first requirement is that of pre-operative medical treatment, to have the patient in the most favorable condition to withstand both the operation itself and the immediate postoperative risks.

Before beginning pre-operative treatment the surgeon should be asked to examine the patient so that he may then determine the wisest surgical program on the basis of the patient's condition when at its worst. He will then not be misled into adopting procedures more radical than the patient might safely be expected to withstand. The importance of this step has just been emphasized by Lahey during the Academy Fortnight.

Physical and mental rest are among the first desiderata in pre-operative medical treatment. The patient should be confined to bed in quiet surroundings and given sufficient sedatives to control his nervousness. The bromids, alone or with hydrated chloral, or the barbiturates such as phenobarbital, amytal, etc., are generally the most satisfactory. The dose should be repeated 3 or 4 times daily and should be just sufficient to produce definite but mild sedation in the given patient. The actual amount will vary rather widely in different patients. It is seldom necessary to resort to the opiates and their use should generally be restricted to the alleviation of severe dyspnea and its attendant mental distress in the first few days of treatment. For this purpose morphin is the agent of choice, and it should be administered hypodermically. The dose should be from 10 to 20 mg. (gr.  $\frac{1}{6}$  to gr.  $\frac{1}{3}$ ). Scopolamin, with or without morphin, has been recommended, but I do not favor it because its actions are untrustworthy, it has a pronounced tendency to cause delirium, and it may produce dangerous respiratory depression. The combination of codein with one of the barbiturates is sometimes beneficial. Sleep should be promoted by hypnotic doses of amytal, chloral, or other simple hypnotic such as paraldehyde. The doses of these agents should be diminished as rapidly as conditions permit and they should be discontinued whenever possible. Their effectiveness is materially enhanced by psychotherapy and reassurance of the patient.

It should be emphasized that the necessity for operation, its comparative safety, and its beneficial results should be discussed with the patient at the very beginning of treatment. His written consent to operation should be secured at this time and the subject then should not be referred to again. In no event should the patient be harrassed by days of anticipation through knowing in advance the date of operation. It was Crile who first taught us the technique and importance of anoci-association and of the procedure dubbed "stealing the thyroid." The lessons learned from these two methods of procedure are as valid today as ever but the radical advances

which have been made in the field of the fixed anesthetics have largely supplanted Crile's more difficult and complicated methods by easier and simpler ones. When the day of operation comes he should be given a basal anesthetic before leaving his bed. The one to be used should preferably be determined in consultation with the surgeon as its choice is in part determined by the type of operation and whether anesthesia is to be local or general.

Diet should be prescribed carefully. Protein probably should be kept close to the basal requirements while carbohydrate is best given in abundance. In emaciated patients a high calory diet should be prescribed to improve nutrition and bring it as early to normal as possible. Patients with much edema should have a restricted salt and water intake, just as in any other type of congestive heart failure. An abundance of glucose should be given during the 24 hours just preceding operation. This is best administered in orange juice or other fruit drinks, and in candy. Abundant fluids must also be taken by the patient shortly before operation. These two steps contribute largely to the prevention of acidosis and dehydration.

Congestive heart failure is dealt with in the usual manner by the use of digitalis and diuretics in addition to the foregoing procedures. About 1.5 gm. (gr. xxij) of a standardized leaf may be given in the first 2 or 3 days, to be followed by maintenance doses of 0.1 to 0.3 gm. (gr. jss to gr. ivss) daily. Almost all patients respond to some extent. Many do so fairly satisfactorily; some to a moderate degree; and others only slightly. This is the case among both the fibrillators and those with regular sinus rhythm, though the former are rather more responsive than the latter. Where anasarca is pronounced resort to the diuretics is often necessary. In my experience much time may be saved by turning at once to the intravenous administration of mersalyl in doses of 0.1 to 0.2 gm. (1 to 2 cc. of the commercial 10% solution); repeated every 3 or 4 days if required. The supplementary administration of ammonium or calcium chlorid is desirable only in obstinate cases. Paracentesis of chest or abdomen rarely is necessary, but should be performed if indicated. Other remedies are in my opinion of value too doubtful to warrant their discussion.

The anginal type is commonly rather unresponsive to treatment by drugs. Immediate relief of the seizure may be had from the nitrites, but they often upset the patient through increasing the tachycardia, palpitation and nervousness, as well as by their common head phenomena in aggravated form. Digitalis is rarely of any value and is likely to increase the frequency, if not the severity of the pain. The greatest help is given by theobromin continued over a period of many days or weeks if well borne. It should always be tried but one should not place too much confidence in its efficacy.

Restoration of normal sinus rhythm is frequently possible in the presence of auricular fibrillation by the administration of quinidin. I do not, however, favor its pre-operative use because return of sinus

rhythm in these patients seldom contributes significantly to the relief of heart failure. Further, the auricular fibrillation often returns promptly following operation with its attendant manipulation of the thyroid gland. Last, many patients spontaneously resume normal rhythm within 10 days or less following thyroidec-tomy. Quinidin is best reserved for postoperative restoration of sinus rhythm in those patients whose fibrillation persists for more than 10 to 14 days. By so using it the normal rhythm is usually resumed promptly and permanently. In some patients the fibrillation is of the fixed type and in these it will either not be checked by quinidin or, if checked, will return shortly after withdrawal of the drug.

These therapeutic procedures should be followed faithfully and persistently so long as improvement in the patient's condition continues. When this point is reached the administration of iodine should begin and be continued until what is apparently optimal improvement has been secured—usually within 10 to 14 days—when the surgeon should take over the patient for immediate operation. The details of the administration of iodine are now so familiar to all that they need not be repeated. Suffice it to say that while Lugol's solution is the form in which it is most often given, the same results may be secured with any of the common preparations such as the syrup of hydriodic acid or the iodides of sodium or potassium. The dose should be adequate but need not be large. Maximal action is secured from 0.6 cc. (min. x) of Lugol's given 3 times daily, or an equivalent amount of iodine in the form of one of the other preparations mentioned.

The administration of iodine usually leads to prompt and rather striking further improvement in the patient's condition, primarily by diminution in thyroid intoxication. This is reflected in further subsidence of the cardiac manifestations. Where the response to other treatment has been more or less satisfactory the institution of iodine therapy may lead to dramatic betterment, often to well nigh complete restoration which, however, seldom endures for long. The marked tendency for the optimal effects of iodine to diminish rather quickly is the chief reason for deferring its use until the period just preceding operation. It is often stated that when one course of iodine has been given, a second is largely ineffective. This is not true in most cases, and if a few weeks be allowed to elapse between courses, the second is generally quite satisfactory in its effects. It must be admitted, however, that the results from the second course are sometimes inferior to those from the first.

The operation is now undertaken when the patient's recovery appears to be optimal, but medical treatment should be prolonged through the early postoperative period, at least to the extent of continuing the iodine, the sedatives as indicated, and the administration of digitalis if there be indications of returning heart failure. Wisdom often dictates the performance of a two-stage thyroidec-tomy. In this event some modification of the medical treatment may



be needed throughout the interval between the 2 operations. The first operation, being generally a hemithyroidectomy, often diminishes the thyrotoxicosis to such an extent that little or no interval medical treatment is required other than diet and the general building up of the patient's nutrition and strength.

Following the completion of subtotal thyroidectomy the most favorable cases will seldom require medical or other treatment beyond the first week, as their cardiac symptoms will have disappeared with the relief of the hyperthyroidism. In the less favorable group the physician will be left with the problem of dealing with one or another type of heart disease uncomplicated by thyrotoxicosis.

**Summary and Conclusions.** 1. Four clinical types of thyrocardiac are recognized: (a) Graves' disease with structurally normal heart; (b) Graves' disease in patients with rheumatic heart disease; (c) thyrotoxicosis in patients with arteriosclerotic or hypertensive heart disease; (d) patients with "masked hyperthyroidism."

2. Emphasis is laid upon thyrotoxicosis as the common factor primarily responsible for the cardiac manifestations in all four types.

3. The relatively unsatisfactory results of cardiac therapy are pointed out.

4. The keystone of successful treatment is shown to be the control of the thyrotoxic state.

5. The minimum of risk and the maximum of success are obtained by pre-operative medical treatment, subtotal thyroidectomy at the most favorable stage and postoperative medical treatment when necessary.

6. Close coöperation between the internist and the surgeon is essential.

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### HODGKIN'S DISEASE MISTAKEN FOR THYROID TUMOR.

BY LESTER M. GOLDMAN, B.S., M.D.,

RESIDENT PATHOLOGIST,  
AND

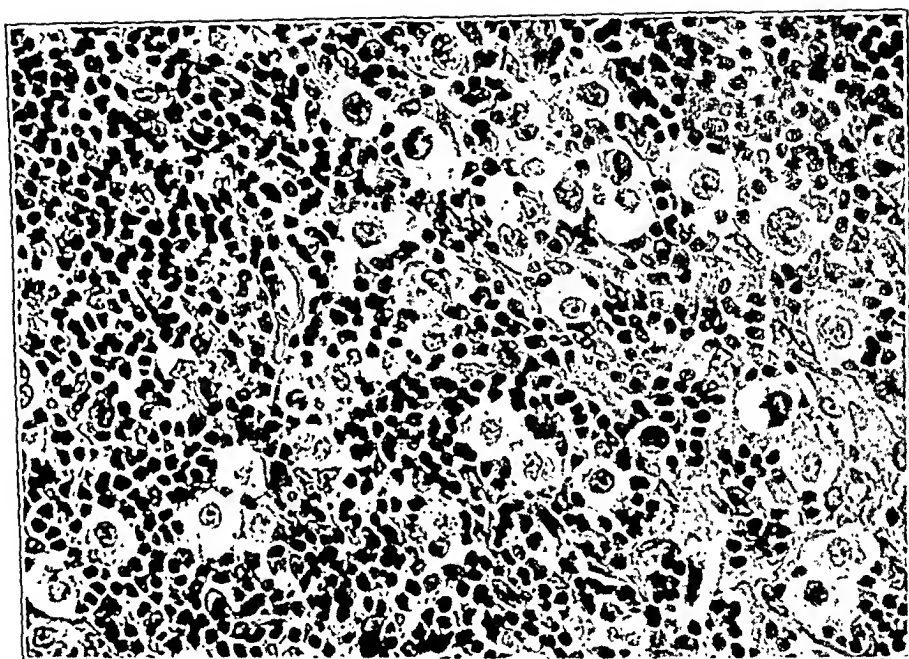
JULES NEWMAN, A.B., M.D.,

VISITING SURGEON.

(From the Laboratory and Surgical Services of the Newark Beth Israel Hospital, Newark, N. J.)

WHILE the infrequency of involvement of the thyroid gland in Hodgkin's disease has been demonstrated in surveys by various authors,<sup>1</sup> it was actually not until the sporadic case reports of Krammer,<sup>2</sup> Lerman,<sup>3</sup> and Warnshuis,<sup>4</sup> that the possibility of mistaking Hodgkin's blastoma for thyroid struma was forcibly pointed out. In reviewing our records we find 2 cases in which such error was made. One of these cases was in the private service of one of the authors.

We shall attempt in this paper to discuss neither the pathology



High-power photomicrograph of section of mass removed in Case 2. This section demonstrates the marked pleomorphism of cells and the presence of large multinucleated cells with fibroblastic proliferation



nor the diagnosis of either thyroid tumors or Hodgkin's disease but merely to present briefly the case histories of these 2 cases and to discuss the importance of realization of the possibility of such diagnostic error.

**Case Reports.** CASE 1.—L. L., female, aged 17, was admitted to the private service of Dr. J. N. on July 4, 1931, with a tumor in the neck and the diagnosis of possible Hodgkin's Disease. History revealed the fact that the patient had first noted a mass in the left side of the neck a month prior to admission, that it had increased progressively in size but presented none of the symptoms of an acute inflammatory process. On physical examination one found a well-developed adult female showing no evidence of emaciation or thyrotoxicosis. There was noted a firm nodular mass in the left side of the neck apparently separated from the thyroid proper. The mass was freely movable, non-tender, and firm in consistency.

Laboratory findings at this time revealed a leukocyte count of 11,000, with 76 per cent polymorphonuclears, 22 per cent lymphocytes, 1 per cent monocytes and 1 per cent basophils. The urine was negative.

On February 5, 1933, the patient was operated upon, a low thyroid incision made, and the prethyroid muscles cut transversely. Two very firm masses, adherent to the surrounding muscles by dense fibrous tissue were found. One mass measuring 2 by 1 inches was located in the region of the left lobe of the thyroid, and the other measuring 1 by  $\frac{1}{2}$  inch in the region of the middle lobe. The operative diagnosis of malignancy of the thyroid gland was made and the patient returned from the operating room.

Subsequently the pathologic report of the tumors removed revealed a typical picture of Hodgkin's lymphoblastoma. Since that date the patient has run the usual malignant course of Hodgkin's disease.

CASE 2.—M. E., female, aged 46, admitted to the private service of Dr. M. D. on July 7, 1933, with a diagnosis of adenoma of the thyroid gland. On admission the patient complained of dyspnea and swelling of the neck of 2 weeks' duration accompanied by a hacking cough. She remained in bed from the time of onset until the time of admission. Her past history was essentially negative. On examination one found a well developed, moderately obese adult female showing no evidence of thyrotoxicosis. There was a firm mass felt in the region of the thyroid isthmus about 3 inches in diameter, which appeared to extend down behind the sternum. There were no other findings of significance.

The blood picture and urine examination on admission were of no significance.

The patient was operated upon on July 8, 1933, at which time thyroidectomy was attempted through a collar incision. The description of the findings at operation were as follows: "The middle lobe of the thyroid was of a hard, almost cartilaginous consistency. It was very firmly adherent to the neighboring structures. There was a distinct encapsulated area, containing some broken down inflammatory material which was in part suppurative in character. The right lobe also seemed enlarged but showed no evidence of any inflammatory process." The middle lobe was removed in small fragments, due to the inflammatory process, and a small portion of the right lobe in addition. The operative diagnosis at this time was subacute thyroiditis.

Cultures from the middle lobe failed to reveal the presence of any organisms. The pathologic diagnosis of the tissue removed was Hodgkin's lymphoblastoma with some thyroid tissue showing little evidence of colloid change.

Roentgen ray of the chest taken after the pathologic report revealed the presence of a mediastinal shadow, probably that of a mass of Hodgkin's nodes.

**Discussion.** While Hodgkin's lymphoblastoma of the thyroid gland is a rarity, Hodgkin's nodes are on the other hand very commonly situated in the region of the thyroid, as in the above 2 cases. In the first case the surgeon appreciated the clinical findings sufficiently to make a correct pre-operative diagnosis, but at operation the tumor was so closely related to the thyroid gland as to make him alter his diagnosis.

The justification for the presentation of these cases is not merely from the standpoint of description of the unusual, but rather to point out a condition which not infrequently leads to an incorrect diagnosis and consequently a very incorrect prognosis. The fact that the subsequent courses and ultimate prognoses of thyroid hyperplasia and Hodgkin's disease are so widely different makes the necessity of correct diagnosis of even greater importance than usual.

**Summary.** 1. Two cases of Hodgkin's disease of the neck mistaken for thyroid tumors are briefly presented.

2. The frequency of this location for Hodgkin's nodes and consequently the great possibility for mistaken diagnosis is pointed out.

3. The importance of correct diagnosis in this particular instance from a prognostic standpoint is emphasized.

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### A CLINICAL COMPARISON OF A PURIFIED GLUCOSIDE AND WHOLE LEAF PREPARATIONS OF DIGITALIS.\*

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THE selection of the most effective digitalis preparation is a problem which constantly confronts the medical practitioner. Much

\* A portion of the funds necessary for this study came from a grant by Hoffmann-La Roche, Inc.

of this perplexity may be relieved by sufficient careful clinical studies of the therapeutic efficacy of various preparations of the drug.

For many years the liquid preparations of digitalis have had widespread use because of historical reasons and official approval at a time when little was known about the chemistry of digitalis. Recently, however, through the realization that infusions and tinctures of the drug might fail in giving full therapeutic effects because of incomplete extraction of the active principles, preparations of the powdered whole leaf of digitalis in tablet, capsule or pill form have become more widely used. This trend has resulted in part from the recommendations of the Digitalis Committee of the American Heart Association.\* Also, during the last few decades, there have appeared a number of special preparations containing only the active principles—the glucosides—of digitalis, claimed to be capable of effecting full therapeutic benefit in dosage more accurately measurable.

In view of the paucity of clinical studies comparing the relative merits of various digitalis preparations, the present study was undertaken in an effort to determine whether or not there is any difference in the therapeutic value of whole leaf as compared with a purified glucoside preparation of digitalis.

*Method of Procedure.* Ambulatory patients (25) with established auricular fibrillation, selected from the Adult Cardiac Clinic of the Pennsylvania Hospital, were divided into 3 groups, similar as to age and degree of circulatory efficiency. One group was given tablets of the whole leaf digitalis, the product of a well-established pharmaceutical house;† the second group received similar tablets prepared by the American Heart Association;‡ and to the third group were administered tablets containing only the extracted and purified glucosides§ of digitalis.

\* Bulletin of the American Heart Association, May, 1930: (1) That tablets or capsules of powdered digitalis leaves be dispensed in all cases where digitalis is indicated, except in emergencies. (2) That such digitalis preparation be standardized by a recognized method of biologic assay, such as the cat or frog, for biologic potency, but that efforts be made to secure uniformity of activity, so far as possible, by adhering to one of these methods of standardization. (3) That the digitalis be further standardized for its absorbability and efficacy by administration to selected patients suffering with auricular fibrillation.

† Digitalis "Tabloids" (Burroughs, Wellcome) are made from the choice leaves of digitalis grown at the Wellcome Materia Medica Farm in England, and are assayed according to the U. S. P. method.

‡ These tablets were prepared under the supervision of Dr. Harry Gold in the Cornell Department of Pharmacology, as follows: 500 pounds of digitalis leaf, finely ground and dried, was obtained from an importer. A specimen was then tested in a few patients with auricular fibrillation in order to ascertain whether it was satisfactorily absorbed and whether it produced therapeutic effects in the average dosage. A portion of the total batch was then made up into compressed tablets by a tablet manufacturer, the strength of the tablets being  $\frac{1}{2}$ , 1, 2 and 3 cat units, respectively. A sample of some of the tablets was then made into a tincture, and the latter again tested by the cat method in order to have an additional check on the potency of the tablets.

§ For the manufacture of Digalen Oral Tablets (Hoffmann-La Roche, Inc.) a quantity of digitalis leaf is dried, finely powdered and biologically assayed. From this quantity the beneficial active principles are extracted and purified by the method of Cloetta. The resultant purified substance is again biologically assayed. The dry powder consisting of the active glucosides is then made into tablets, so that each tablet is of  $\frac{1}{2}$  cat unit potency. The strength of the finished tablets is further checked by re-assay by the cat method.

Table 1 gives a summary of the 25 cases that were followed during the entire course of the study. These cases ranged in age from 23 to 79 years. There were 3 cases in the third decade, 6 in the fourth, 6 in the fifth, 6 in the sixth, 3 in the seventh, and 1 in the eighth. There were 16 males and 9 females. Rheumatic fever\* was considered the underlying cause of the heart disease in 18 cases (72%); 2 of these cases also had hypertension and 1 had both hypertension and marked arteriosclerosis; arteriosclerosis was the etiologic agent in 6 cases (24%); 2 of these had associated hypertension; thyroid heart disease was present in 1 case (4%). The average age of the rheumatic group was 40 years; of the arteriosclerotic group, 62 years. In no case was syphilis considered to be an etiologic factor in the heart disease. A positive Wassermann reaction was present in only 1 case.

TABLE 1.—SUMMARY OF ETIOLOGIC FACTORS, PHYSICAL FINDINGS AND DIGITALIS DOSAGE IN 25 CASES OF ESTABLISHED AURICULAR FIBRILLATION.

Case.	Age.	Sex.	Etiologic classification.*	Conges- tive failure.	Vital capacity (av'ge).	Blood pressure (av'ge).	Average cardiac area (sq. cm.). Actual : predicted.	Daily maintenance dose of digitalis (grains).
7	42	F	Doubtful (M.S.)	++	1400	125/80	123 : 100	Dig 1½ : AHA 1½
16	28	F	Rheumatic fever (M.S.)	+	1800	110/75	125 : 90	Dig 1½ : AHA 1½
18	54	M	Arteriosclerosis	++	1900	100/110	175 : 106	Dig 1½ : AHA 1½
21	49	F	Doubtful (M.S.)	+++	2200	140/80	169 : 00	Dig 1½ : AHA 1½
23	53	F	Rheumatic fever (M.S.)	+	1300	100/60	141 : 80	Dig 1 : AHA 1
1	60	M	Rheumatic fever (M.S.)	+	3150	175/105	175 : 105	Dig 2 : BW 3
13	30	M	Rheumatic fever (M.S.)	+	2200	110/75	153 : 00	Dig 1½ : BW 1½
20	33	F	Doubtful (M.S.)	0	2000	90/60	90 : 92	Dig 1½ : BW 1½
22	50	M	Doubtful (M.S.)	0	2500	110/70	121 : 96	Dig 1½ : BW 1½
5	53	F	Rheumatic fever (M.S.)	++	1800	150/80	123 : 87	AHA 1 : Dig 1
9	46	M	Rheumatic fever (M.S.)	+++	2300	125/80	155 : 102	AHA 2½ : Dig 2½
10	45	F	Rheumatic fever (M.S.)	0	2000	170/100	119 : 92	AHA 1½ : Dig 1½
11	47	M	Arteriosclerosis (?)	+	2600	140/80	113 : 99	AHA 1 : Dig 1
17	79	M	Arteriosclerosis	+++	2100	180/80	167 : 111	AHA 1 : Dig 1
19	39	F	Doubtful (M.S.)	++	1400	110/60	133 : 90	AHA 1½ : Dig 1½
12	50	M	Thyroid	0	2700	125/75	114 : 95	AHA 1½ : BW 1½
14	38	M	Rheumatic fever (M.S. A.I.)	0	3400	120/70	129 : 107	AHA 3 : BW 3
24	67	M	Arteriosclerosis	++	1500	120/80	123 : 90	AHA 3 : BW 3
2	26	F	Doubtful (M.S.)	0	2800	105/65	165 : 108	BW 1 : Dig 1½
6	69	M	Arteriosclerosis	++	2400	135/90	130 : 116	BW 2½ : Dig 1½
8	31	M	Doubtful (M.S.)	0	2700	110/70	91 : 91	BW 1½ : Dig 1½
15	40	F	Doubtful (M.S.)	0	2200	120/70	114 : 99	BW 1½ : Dig 1½
25	36	M	Rheumatic fever (M.S.)	0	3100	120/65	101 : 106	BW 1½ : Dig 1½
3	23	M	Rheumatic fever (M.S. A.I.)	++	2600	120/35	195 : 104	BW 1 : AHA 1
4	58	M	Arteriosclerosis	0	2500	125/60	92 : 94	BW 3 : AHA 3

\* No history of polyarthritis or chorea in cases classified as "doubtful."

M.S. = Mitral stenosis. A.I. = Aortic insufficiency. Dig = Digalen. BW = Burroughs, Wellcome & Co. AHA = American Heart Association.

The clinical course of the 3 groups was followed for 9 months on the 3 respective preparations of digitalis. During the subsequent 6 months, 4 of the 9 members of the group which had previously received the preparation containing only the glucosides were changed

\* In this group are included all cases of mitral stenosis. Several of these cases who did not have a history of polyarthritis or chorea are classed etiologically as "unknown."

to the commercial whole leaf tablet, and the others were given the American Heart Association product; 5 of the 7 patients originally given the commercial whole leaf product were changed to the glucoside preparation, and the remainder was given the A. H. A. product; 6 members of the group started on the A. H. A. product were then placed on the glucoside tablet, and 3 were given the commercial whole leaf product. Each patient reported to the Cardiac Clinic at intervals of from 1 to 4 weeks for a check-up of symptoms and a physical examination, which included a vital capacity determination. Orthodiagraphic and electrocardiographic studies were made every 3 or 4 months.

TABLE 2.—RELATIONSHIP OF CARDIAC ENLARGEMENT AND CONGESTIVE FAILURE.

Degree of cardiac enlargement.	Total cases.	Degree of congestive failure.*	Cases.
1. Marked . . . . .	10	Severe (+++)	3
		Moderate (++)	3
		Slight (+)	3
		None (0)	1
2. Moderate . . . . .	11	Severe (+++)	0
		Moderate (++)	4
		Slight (+)	2
		None (0)	5
3. No enlargement . . . . .	4	Severe (+++)	0
		Moderate (++)	0
		Slight (+)	0
		None (0)	4

\* In none of the cases was the degree of congestive failure materially altered during the study.

In Table 2 the degree of cardiac enlargement is classified with signs of congestive failure. Râles at the lung bases, enlargement of the liver and edema of the lower extremities in addition to dyspnea on exertion were considered signs of congestive failure. In 4 cases (aged 31, 33, 36 and 58 years, respectively), there was no evidence of cardiac enlargement on physical or Roentgen ray examination. None of these 4 showed any signs of a failing circulation. In general, there seemed to be a direct relationship between the degree of cardiac enlargement and signs of congestive failure, in this small series.

The following case histories and clinical data are given in brief, as examples of the type of cases used and the character of the observations made.

**Case Abstracts.** CASE 6.—P. F., Jewish male, aged 69, of sthenic build, formerly a cabinet maker, with no history of illnesses etiologically associated with cardiac disease, first noticed fatigue, palpitation, dyspnea and orthopnea in 1922 (aged 56). He was enrolled in Cardiac Clinic in 1924, when marked cardiac enlargement, regular sinus rhythm, peripheral edema, normal blood pressure and pulmonary emphysema were found present. In October, 1925, he was admitted to the hospital in congestive failure, with auricular fibrillation; and digitalis therapy was instituted. At that time,



and on two subsequent hospital admissions (November, 1926, and June, 1927, respectively), regular sinus rhythm was restored (for periods of several months) by the use of quinidin. He has not been able to work steadily since 1925. On his last two hospital admissions (November, 1931, and January, 1933) he presented auricular fibrillation with symptoms of moderate cardiac failure.

*Cardiovascular Diagnosis.* (A) Arteriosclerosis, pulmonary emphysema; (B) cardiac enlargement, fibrosis of myocardium, left ventricular preponderance; (C) chronic auricular fibrillation; (D) Class 2b.

#### CASE 6: P. F., WHITE MALE, AGED 69, MARRIED.

Etiologic classification:		Arteriosclerosis.					
Brand of digitalis:		Burroughs, Wellcome & Co.			Digalen.		
Date:		3/10/32.	6/16/32.	10/6/32.	1/12/33.	2/2/33.	4/6/33.
Average daily dose (gr.)		2½	2½	2½	*	1½	1½
Weight (lbs.)		209	196	197	193	186½	193½
Ventricular rate		82	86	72	168	92	84
Pulse rate		82	70	72	96	92	84
Dyspnea		++	++	0	++++	+	+
Edema		0	0	0	0	0	0
Lungs (rales)		0	0	0	++	0	0
Liver (cms. palp. M. C. L.)		0	0	0	0	0	0
Blood pressure		138/90	140/90	135/90	..	134/80	140/90
Vital capacity (cc.)		2350	2200	2600	1600	2600	2400

\* The patient, having neglected to take digitalis for 3 weeks, was hospitalized on this date because of signs and symptoms of early congestive failure.

CASE 15.—B. K., an obese, Hungarian housewife, aged 40, with no history of illnesses etiologically associated with heart disease, had no cardiac symptoms until February, 1930. At that time—during the last month of a pregnancy—she developed palpitation, orthopnea and peripheral edema; and physical examination revealed auricular fibrillation with a short, soft, blowing diastolic murmur at the apex. Digitalis therapy, started at that time, has been continued without interruption. She has attended Cardiac Clinic since March, 1930. During the past 3 years she has been able to perform her household duties, complaining only of easy fatigue and slight dyspnea on exertion.

*Present Cardiovascular Diagnosis.* (A) Unknown; (B) mitral stenosis, cardiac enlargement, left ventricular preponderance; (C) chronic auricular fibrillation; (D) Class 2a.

#### CASE 15: B. K., WHITE FEMALE, AGED 40, MARRIED.

Etiologic classification:		Unknown (mitral stenosis).					
Brand of digitalis:		Burroughs, Wellcome & Co.			Digalen.		
Date:		12/10/31.	3/24/32.	7/14/32.	10/20/32.	1/19/33.	4/13/33.
Average daily dose (gr.)		2.25	1.07	1.07	1.07	1.07	1.07
Weight (lbs.)		203	192½	184½	189½	198½	190½
Ventricular rate		84	70	72	76	64	76
Pulse rate		84	70	72	76	64	76
Dyspnea		0	0	0	0	0	0
Edema		0	0	0	0	0	0
Lungs (rales)		0	0	0	0	0	0
Liver (cms. palp. M. C. L.)		0	0	0	0	0	0
Blood pressure		135/80	145/85	130/85	120/70	120/74	120/72
Vital capacity (cc.)		2400	2100	2550	2100	2200	2300

CASE 16.—M. L., a Jewish housewife, aged 28, with a history of tonsillitis at 10 years, rheumatic fever at 14 and 18 years, and attacks of pneumonia at 18, 19 and 20 years, respectively. Directly after the second attack of rheumatic fever, 2 weeks (January 14 to February 4, 1923) were spent in the hospital suffering palpitation and orthopnea. Physical examination revealed mitral stenosis, mitral insufficiency and cardiac enlargement; and digitalis therapy was begun. In November, 1928, she was enrolled in the Cardiac Clinic. In June, 1929, she suffered left hemiplegia, which completely disappeared within 36 hrs. In May, 1930, right hemiplegia with motor aphasia developed; and the aphasia has persisted to date. Auricular fibrillation was first diagnosed in July, 1929. During the past few years she has been kept fairly free of congestive phenomena under digitalis therapy; but her exertion tolerance is very poor.

*Present Cardiovascular Diagnosis.* (A) Inactive rheumatic fever; (B) mitral stenosis, mitral insufficiency, cardiac enlargement; (C) chronic auricular fibrillation; (D) Class 2b.

CASE 16: M. L., WHITE FEMALE, AGED 28, MARRIED.

Etiologic classification:		Rheumatic fever.					
Brand of digitalis:		Digalen.			Am. Heart Assn.		
Date:		12/17/31.	3/17/32.	7/7/32.	10/6/32.	1/5/33.	4/13/33.
Average daily dose (gr.)		1½	1½	1½	1½	1½	1½
Weight (lbs.)		126	127½	123½	126½	126	125½
Ventricular rate		80	68	80	96	80	84
Pulse rate		80	62	74	96	80	84
Dyspnea		0.	0	0	0	0	0
Edema		0	0	0	0	0	0
Lungs (râles)		0	0	0	0	0	0
Liver (cms. palp. M. C. L.)		0	0	0	0	0	0
Blood pressure		126/72	125/75	118/68	120/70	125/78	105/65
Vital capacity (cc.)		1800	1500	1600	2000	1600	1900

BIOASSAY. To make certain of the potency of the preparations used, Dr. John Reisinger, of the Pharmacology Department of the University of Pennsylvania kindly performed a bioassay of the 3 preparations used in the clinic. The potency was not compared with any standard preparation such as the International Digitalis powder, but simply the relative potencies of the 3 preparations per tablet. In the case of Digalen, the manufacturers state the potency in cat units per tablet, and our results are expressed as the number of tablets per cat unit and as a fraction of a cat unit per tablet. The potency of the other preparations is similarly expressed as a fraction of a cat unit per tablet since the drugs were dispensed on the assumption that each tablet contained 0.1 gm. digitalis with a potency of approximately 1 cat unit.

The cat method technique of C. de Lind van Wijngaarden (*Arch. exp. Path. u. Pharmacol.*, 113, 40, 59, also 114, 21, 1926) as described by Burns (*Methods of Biological Assay*, Oxford University Press, 1926) was used. The average lethal dose per kg. of cat of a hot water infusion for 5 cats is given for each preparation expressed in grams of the powdered tablet or in the number of tablets in the case of Digalen, since each tablet is said to contain ½ cat unit. The probable error is expressed as twice the standard deviation.

Preparation.	Lethal dose per kg. of cat. Powdered tablet.	Weight of tablet.	Cat units per tablet.	Relative potency.
American Heart Association	0.165 gm. ± 0.033	0.113 gm.	0.68	70%
Burroughs, Wellcome & Co.	0.185 gm. ± 0.045	0.160 gm.	0.86	89%
Digalen	2.06 tablets ± 0.40	"½ CU"	0.48	100%
		(Manufacturer's assay)		

This assay indicates that the Digalen tablets under our laboratory conditions were practically the strength claimed for them by the manufacturers; namely,  $\frac{1}{2}$  cat unit per tablet. The A. H. A. and Burroughs, Wellcome tablets used contained less than 1 cat unit each and, compared with 2 tablets of Digalen (1 cat unit) as 100%, were 70% and 89% as potent, respectively.

**RESULTS.** No striking difference was observed in the general clinical picture, including the ability to work, of the members of the 3 groups. However, during the course of the study, before the summarization of our results, and before bioassay was done, it was our impression that the preparation of the extracted purified glucosides was somewhat more effective per *stated* unit of dosage than either of the two whole leaf preparations. Final analysis of the data tended to substantiate that idea, since in 5 (25%) of the 20 cases given the purified glucoside preparation the daily maintenance dosage, measured in cat units, was smaller than that of either of the whole leaf preparations. This result may be explained by the relatively greater strength of the purified glucoside tablet as revealed by the bioassay. No difference was detected in the dosage per cat unit of the two whole leaf preparations.

The progress of each case was based upon the sense of well-being, the ventricular rate, the pulse deficit, the physical signs of congestive failure, and the vital capacity. In the cases with increase of congestive failure, a relationship was observed between the diminution of vital capacity on the one hand, and the increase in weight, with edema and hepatic engorgement, on the other. No consistent significant changes were observed in the orthodiagraphic studies. We appreciate that such uncontrollable factors as the progression of the pathologic lesions, lack of coöperation in following the prescribed dosage of digitalis or the suggested amount of physical effort, and the development of concomitant infections may affect the circulatory reserve and render the interpretation of results difficult.

In making such a study it must be remembered that there exists in the majority of patients with established auricular fibrillation a fairly wide margin between the minimum dosage necessary for optimum digitalization and the maximum dosage which can be tolerated without the incidence of toxic effects.

Since the bioassay reveals a greater potency per unit of dosage in the case of the purified glucoside preparation, it is impossible to determine whether the slightly smaller cat unit dosage necessary with this preparation, in a few cases, was the result of this factor or of better absorption, better fixation in the heart muscle or a combination of these factors.

**Summary and Conclusions.** 1. Twenty-five ambulatory cases of established auricular fibrillation were divided into three similar groups: one group was given a preparation of the extracted, purified glucosides of digitalis; another was given a whole leaf preparation

manufactured by a well-established pharmaceutical house; and the third group received whole leaf tablets prepared by the American Heart Association. The groups were followed clinically for 9 months and then, after interchanging the preparations, for another period of 6 months.

2. No significant difference could be ascertained in the clinical pictures of the patients in the 3 groups during the period of observation.

## THE MECHANISM OF THE EARLY RELIEF OF PAIN IN PATIENTS WITH ANGINA PECTORIS AND CONGESTIVE FAILURE AFTER TOTAL ABLATION OF THE NORMAL THYROID GLAND.\*†

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WE wish to report observations on the mechanism of the early relief of pain in many patients with angina pectoris and congestive failure immediately after complete removal of the normal thyroid gland. Three syndromes were studied: the characteristic syndrome of angina pectoris (Heberden), precordial pain other than angina and the hyperesthesia and hyperalgesia of the chest wall frequently associated with the various forms of chronic heart disease. In accord with the clinical studies of the circulation which formed a rational basis for removal of the normal thyroid gland in congestive failure and angina pectoris,<sup>6-10</sup> the most striking relief of chest pain has been concomitant with the lowering of the metabolic rate and decrease in the work of the heart as gauged by measurements of the velocity of blood flow.<sup>3, 11, 12, 22</sup> Not infrequently, however, chest pain, experienced constantly for months to years, has disappeared immediately after operation when the metabolic

\* This is the sixth study of the treatment of chronic heart disease by producing a subnormal metabolic rate in patients with no evidence of thyrotoxicosis.

† Read in part at the meeting of the American Society for Clinical Investigation at Atlantic City, April 30, 1934.

rate was still unchanged. Of 50 patients with angina pectoris or congestive failure, 20 definitely have shown this early postoperative relief of pain. The present communication deals with observations only on these patients.

The effect of operation on the distribution of pain and on other characteristics of the attacks was studied when the patients were exercised under standardized conditions.<sup>41</sup> Precordial pain other than that characteristic of angina pectoris was experienced at complete bed rest in almost all of the 20 cases of congestive heart failure and angina pectoris. The pain varied in character and location in different patients and was characterized as "dull," "heavy," "gripping," "tender," "pressing," "knife-like," "crushing," "tearing," "sticky like needles." It was referred to the sternum, the xyphoid, the left or right chest. The areas of skin hyperesthesia and muscle tenderness varied greatly in extent, in some patients being narrowly localized, in others being rather widespread. In a given patient, however, the characteristics of the painful areas were constant. These symptoms have long been accurately described by clinicians, particularly by Morgagni,<sup>41</sup> Laennec,<sup>30</sup> Hope,<sup>27</sup> Gibson,<sup>23</sup> Maekenzie,<sup>35</sup> Lewis,<sup>33</sup> White<sup>56</sup> and Swetlow.<sup>50</sup>

**Methods.** Observations on the radiation of pain and the symptom complex of angina pectoris were made immediately after an attack had been produced by exercise in the cold. These observations were verified frequently before and after operation. The observations reported on non-anginal precordial pain were made only on patients who could be relied on for accurate and intelligent reports and in whom there was no evidence of other etiological factors. The type, frequency, duration and intensity of such precordial pain were particularly noted. The observations were made independently by several observers and were checked repeatedly before and after operation. Every attempt was made to avoid suggestion during examination or interrogation. Skin hyperesthesia was tested by cotton, pinch, scratch and pin prick. Hyperalgesia of the thorax was tested by finger pressure; muscle tenderness was tested by pinching.

The early postoperative relief of pain is exemplified by the clinical course of patient G. F., the first patient in whom complete removal of the normal thyroid gland was performed for relief of angina pectoris and congestive heart failure.<sup>11</sup>

*Clinical Abstract.* For many months this patient (G. F.) had suffered attacks of stabbing pains over the left precordium and scapula, radiating over both shoulders and down the inner aspects of both arms. The pain was increased by exercise, diminished by rest and relieved by nitroglycerin. During the 6 months prior to admission this patient also noted a constant sense of pressure in the chest and continuous ache over the precordium. Immediately after operation all the above-mentioned pains vanished. The pains remained absent, although no sedative was administered after the 3d postoperative day. The basal metabolic rate on the 7th postoperative day was  $-7\%$ , as compared with the pre-operative rate of  $-2\%$ . Between the 2d and 5th postoperative week the pain on exercise referable to the left shoulder recurred, but disappeared permanently as the basal metabolic rate fell to  $-28\%$ .

TABLE 1.—EARLY RELIEF OF PAIN IN CHRONIC HEART DISEASE.

Case.	Date of operation.	Age, yrs.	Diagnoses.*	Pre-op. B.M.R., %	Pre-operative chest discomfort.	Observed disappearance of pain postoperative.†		Partial or complete recurrence of pain postoperative.		Final disappearance of pain postoperative.	
						Time.	B.M.R., %	Time.	B.M.R., %	Time.	B.M.R., %
1. G. F.	12/15/32	32	Rheumatic heart disease; congestive failure; coronary thrombosis and angina pectoris	-2	Constant pain over sternum and stabbing over precordium to left scapula; aching in both arms, over at rest (2 yrs.)	1 day	-7 week post-op.	14 days	-10	5 weeks	-28
2. E. W.	11/21/33	27	Rheumatic heart disease; congestive failure	+5	Frequent palpitation and precordial pain (3 yrs.)	3 days	+5 11th day	None	...	...	...
3. R. D.	3/25/33	23	Rheumatic heart disease; auricular fibrillation; congestive failure	-3	Constant pressure over precordium at rest (10 yrs.)	2 days	...	None	...	...	...
4. F. C.	4/18/33	31	Cor pulmonale; congestive failure	-4	Pounding, constant sense of pressure pain over heart at rest (5 yrs.)	4 days	-10 10th day	None	...	...	...
5. W. B.	7/ 6/33	61	Arteriosclerotic heart disease; congestive failure	-10	Pounding of heart, continuous stabbing ache over precordium at rest (1 yr.)	3 days	...	15 days	...	8 weeks	-32
6. F. Z.	9/14/33	21	Rheumatic heart disease; cardiac asthma	-1	Intense subasternal constriction, pain, severe dyspnea occurring at rest (8 mos.)	4 days	...	...	...	...	...
7. B. R.	7/28/33	48	Rheumatic heart disease; congestive failure	+3	Tightness of chest and "bearing down feeling" over precordium at rest (2 yrs.); stabbing pain over left breast (3½ yrs.)	1 day	-10 30th day	None	...	...	...
8. M. C.	7/21/33	57	Arteriosclerotic heart disease; angina pectoris; coronary thrombosis	-24	Dull ache in left shoulder; steady pain over precordium at rest (3 yrs.)	1 day	-26 12th day	12th week	-34	...	...
9. M. F.	6/30/33	50	Arteriosclerotic heart disease; angina pectoris; coronary thrombosis	-14	Sharp precordial pain following small meals (2 yrs.); precordial pain at rest daily	1 day	-17 16th day	9th day	...	4 weeks	-31
10. F. D.	8/25/33	18	Rheumatic heart disease; congestive failure	-12	Sharp "stabbing" precordial pain pounding when lying on left side (16 mos.)	1 day	...	...	...	...	...
11. G. O.	7/31/33	65	Hypertensive heart disease; angina pectoris	-13	"Bands across chest," 5 to 6 times a day at rest; knife-like pain in back after meals (8 yrs.)	1 day	...	12 days	...	8 weeks	-35
12. M. W.	7/21/33	54	Arteriosclerotic heart disease; angina pectoris; coronary thrombosis	-7	Subasternal pressure, "choking feeling" attacks of pain at rest over precordium "like knife put in and turned" (8 yrs.)	1 day	-12 10th day	None	...	...	...
13. H. G.	8/26/33	22	Rheumatic heart disease; congestive failure	+7	Sharp "sticky" pain over heart, coming on 1 to 2 times a day while at rest (1 yr.)	1 day	...	None	...	...	...
14. G. M.	12/15/33	45	Rheumatic heart disease; congestive failure	-6	Marked tenderness to pressure over localized area, 5th rib anteriorly	2 hours local anes.	-11 8th day	None	...	...	...

\* All patients with rheumatic heart disease showed the signs of mitral stenosis.

† The "Time of Disappearance of Pain" refers to time at which first observations were made.

A resumé of our findings in regard to the early relief of non-anginal precordial pain in 14 patients after complete ablation of the thyroid gland is given in Table 1. Of the 14 patients, 9 experienced unquestioned relief within 24 hours after operation; in 4 of the 14, pain recurred within a few weeks, followed by permanent disappearance at varying intervals of time as the basal metabolic rate dropped. In 1 patient (M. C.), the basal metabolic rate was low before operation and showed only a moderate further reduction. The precordial pain in this subject persisted except for a period of marked relief during the first postoperative week.

As an increasing number of patients stated that precordial pain disappeared soon after operation, it became difficult to believe that this relief was due to suggestion. The influence of postoperative sedation was eliminated as a causal factor. The possible effects of general anesthesia were obviated by examination within 2 hours after operation conducted under local novocain infiltration. These observations led us to review the current concepts of the nature of precordial pain in patients with chronic heart disease.<sup>19, 29, 34, 35</sup>

It is generally held that the symptom complex of angina pectoris and precordial pain and chest hyperalgesia in other forms of chronic heart disease have a common underlying neural pathway. Under normal physiologic conditions, a constant stream of impulses is conveyed by the visceral afferent nerves from the heart to the spinal cord. If, because of a cardiac lesion, excessive stimuli bombard a certain segment of the spinal cord, an irritable focus is produced in the nerve centers of the segment. Normal afferent impulses from skin and muscle of the chest wall that happen to traverse this same irritable cord segment become augmented. It is these impulses that are appreciated in the sensorium as pain. Since these impulses normally travel from the chest wall to the spinal cord, the pain is naturally referred to the chest. Further stimulation of such skin areas by touch or pressure merely augments the normal skin impulse; and heightened sensitivity, hyperesthesia or actual tenderness is thus produced. If cardiac afferent pathways are interrupted, the "irritable focus" subsides and hyperalgesia and pain disappear.

The hypothesis that the early relief of hyperesthesia and hyperalgesia of the chest is due to interruption of cardiac afferent nerve pathways was tested by more detailed pre-operative and post-operative studies in several patients. Three intelligent and coöperative patients who were chosen had severe localized symptoms and signs. One patient suffered from angina pectoris, another from angina pectoris and congestive heart failure and the 3d from angina pectoris induced by attacks of paroxysmal auricular fibrillation. The night before operation, each of the areas of skin sensitivity and spots of local tenderness were accurately mapped out with indelible ink. Two, and again 9 hours after operation, observations were made by different observers on changes in hyperesthesia and

hyperalgesia. These observations were repeated daily during the patient's stay in the hospital. A brief resumé of our findings is given below:

CASE 15.—*Rheumatic heart disease, mitral stenosis and insufficiency, paroxysmal auricular fibrillation. Loss of hyperesthesia and diminution in hyperalgesia of the chest after total thyroidectomy. Return of all signs in 22 days before basal metabolic rate dropped. Permanent loss of hyperesthesia and hyperalgesia coincidental with fall in basal metabolic rate.* M. G., a female, aged 49, was admitted with the diagnoses of rheumatic heart disease and paroxysmal auricular fibrillation. She complained of severe "pressing and crushing" epigastric pain, radiating to both scapulæ and associated with a "choking" sensation in the neck, combined with the paroxysmal auricular fibrillation. Examination showed hyperesthesia and areas of localized precardial tenderness. (Fig. 1, a.) Light pressure on these areas made her wince. Pre-operatively, the basal metabolic rate was +3%.

Two hours after operation, performed under local anesthesia, November 24, 1933, the patient developed paroxysmal fibrillation, associated with an "uncomfortable" feeling under the sternum. She was surprised to note that for the first time in 2 years the attack was not accompanied by crushing pain. Pressure over spots, previously very tender, gave rise only to a dull ache. Hyperesthesia over the left chest anteriorly and posteriorly had disappeared completely. (Fig. 1, b.) During the next 10 hours the patient was given no sedation. At 9 p.m., on the day of operation, the patient was alert and the above-mentioned observations were corroborated. These findings remained constant during the next 10 days, examination being made in the morning and late afternoon. She stated that "her heart felt quieter and lighter." From the 11th to the 22d day after operation, hyperesthesia and tenderness over localized bone areas gradually returned to their pre-operative intensity. (Fig. 1, c.) Periosteal hyperalgesia and skin hyperesthesia were present as before operation. Seven weeks after operation, hyperesthesia and hyperalgesia had disappeared. The basal metabolic rate at this time was -16%.

CASE 16.—*Coronary sclerosis, angina pectoris of 2 years' duration. Loss of hyperesthesia after total thyroidectomy. Loss of hyperalgesia of bone and muscle coincident with fall in basal metabolic rate.* M. S., male, aged 46, entered the hospital because of attacks of "crushing," viselike pain under the xyphoid, radiating to the back and left arm, associated with a "choking" sensation in the throat brought on by exertion, emotion and ingestion of food. On examination the left chest anteriorly and posteriorly was hyperesthetic to pin prick, cotton, pinch, heat and cold. A spot painful to pressure was present over the left 4th rib anteriorly. (Fig. 2, a.) The left sternomastoid and trapezius muscles were tender to pressure. The basal metabolic rate pre-operatively was -8%. Nine hours after operation (November 25, 1933, gas-oxygen), the skin hyperesthesia had disappeared but the bone and muscle tenderness were still present. (Fig. 2, b.) This finally disappeared 21 days postoperatively, when the basal metabolic rate had decreased to -18%. (Fig. 2, c.)

CASE 17.—*Rheumatic heart disease, mitral stenosis and regurgitation. Loss of hyperesthesia and hyperalgesia of chest after left hemithyroidectomy. Return of all signs 6 weeks after operation.* R. S., a male, aged 41, was admitted with the diagnoses of mitral stenosis and regurgitation, aortic insufficiency, coronary thrombosis and angina pectoris. The pre-operative distribution of skin hyperesthesia, bone and muscle tenderness is indicated in Fig. 3, a. The basal metabolic rate was +8%. On November 28, 1933, the left lobe of the thyroid gland was removed under local novocain anesthesia. Two hours after hemithyroidectomy, hyperesthesia and muscle tenderness had disappeared. (Fig. 3, b.) After 2 weeks there was a



gradual return of hyperesthesia and hyperalgesia until all signs had returned to their pre-operative level. (Fig. 3, c.) Six weeks after operation, the basal metabolic rate was +3%.

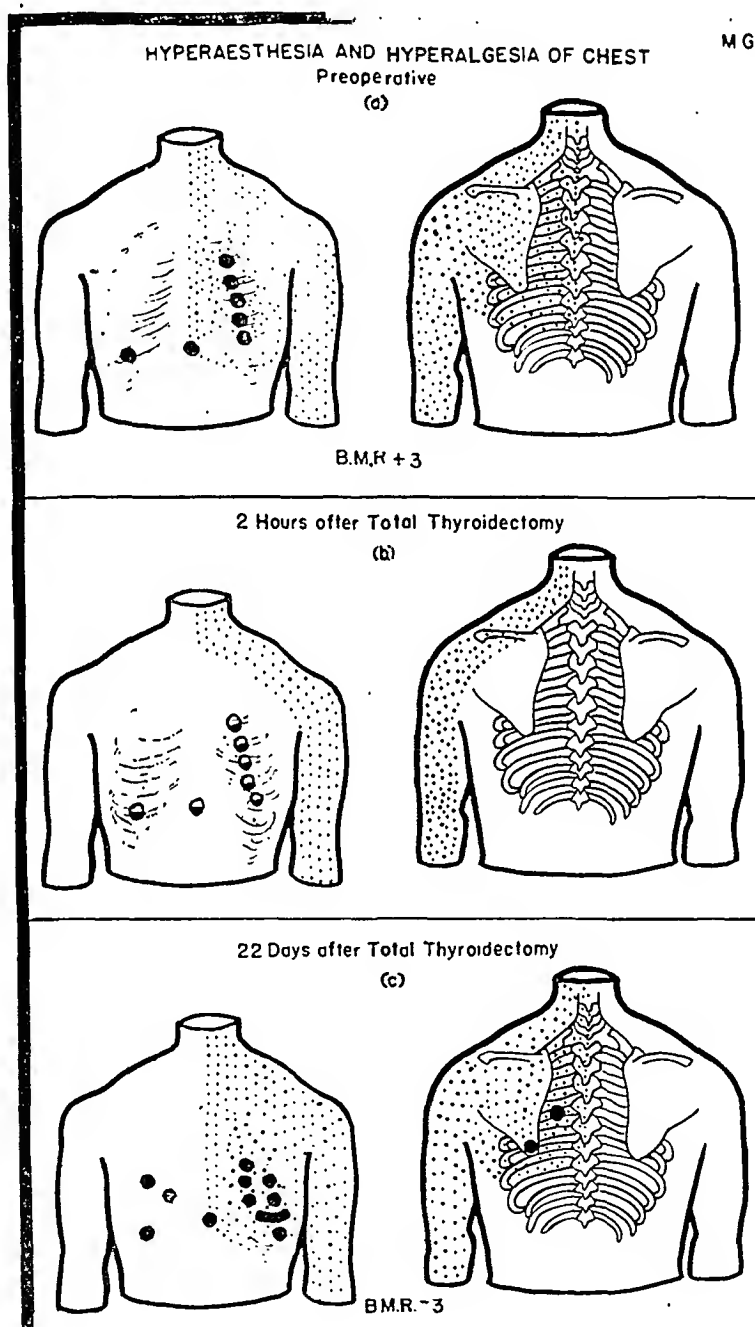


FIG. 1.—Case 15. Loss of hyperesthesia of chest immediately after total thyroidectomy with return of skin hypersensitivity 11 to 22 days postoperatively, before the basal metabolic rate had dropped markedly. Dots indicate regions of hyperesthesia; solid black areas indicate points of bone tenderness. Circles indicate lessened periosteal tenderness.

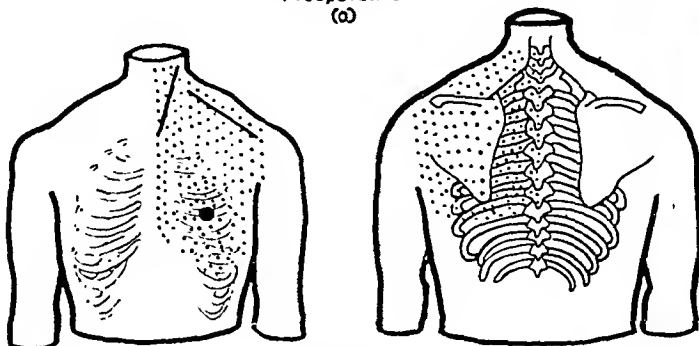
These 3 patients showed prompt relief of hyperesthesia, hyperalgesia and muscle tenderness referable to certain localized areas, which had been regularly present before operation. These areas

## HYPERAESTHESIA AND HYPERALGESIA OF CHEST

M.S.

Preoperative

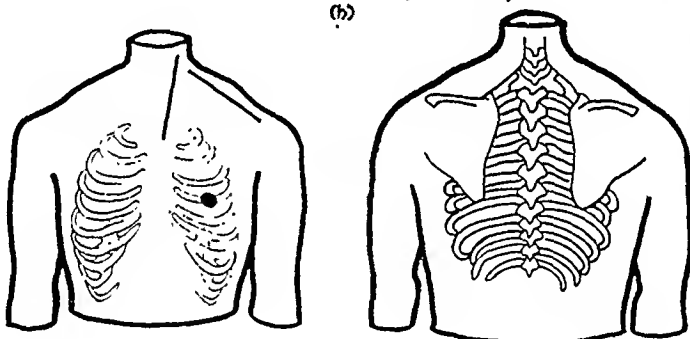
(a)



B.M.R. +8

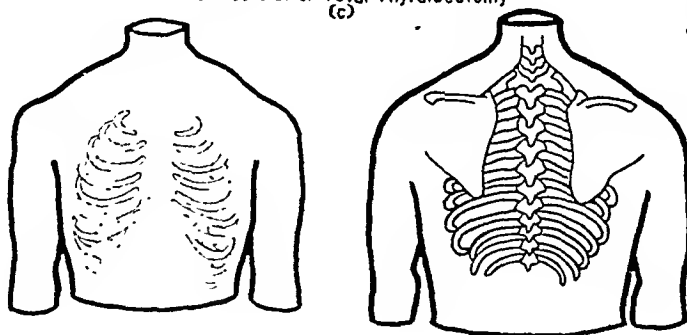
9 Hours after Total Thyroidectomy

(b)



3 Weeks after Total Thyroidectomy

(c)



B.M.R. -18

FIG. 2.—Case 16. Immediately after total thyroidectomy, persistent loss of hyperesthesia. Loss of muscle and bone tenderness coincident with reduction of the basal metabolic rate. Dots indicate regions of hyperesthesia; solid black area indicates bone tenderness. Lines indicate muscle tenderness.

again became hyperesthetic a few weeks after total thyroidectomy. Only after the basal metabolic rate showed a marked lowering did hyperesthesia and hyperalgesia disappear permanently.

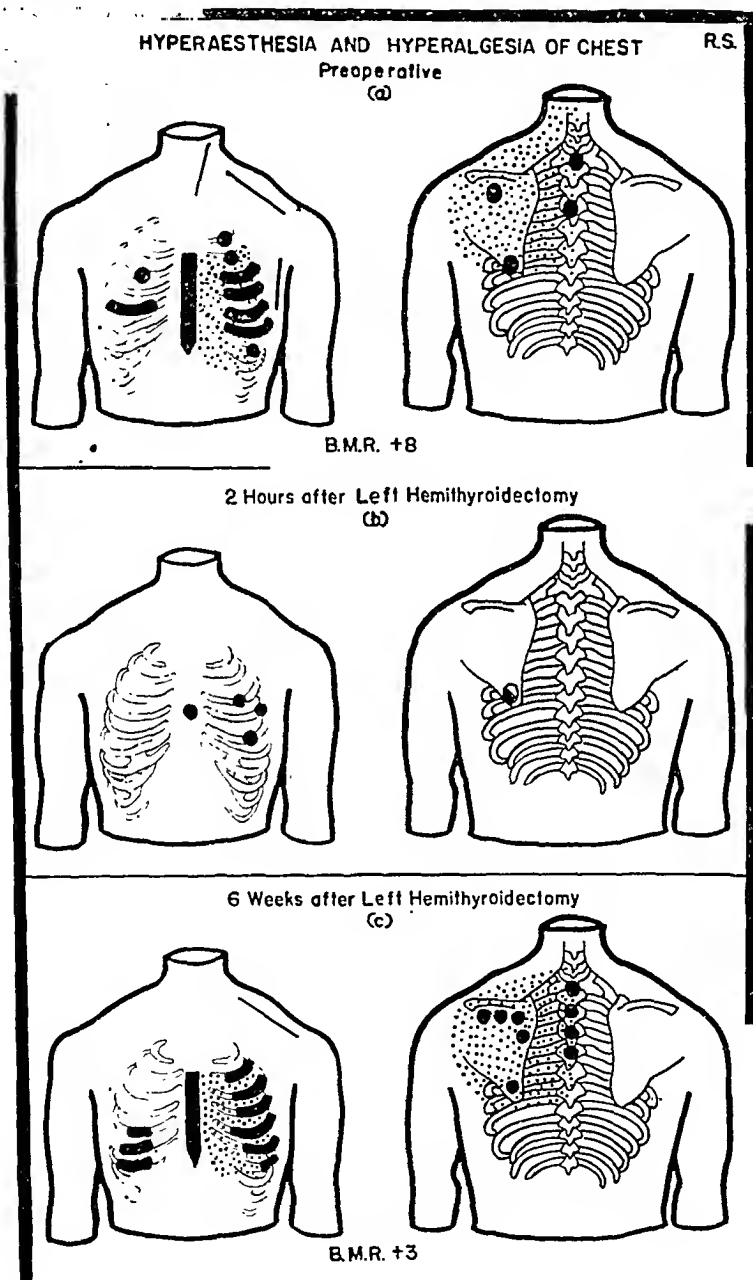


FIG. 3.—Case 17. Immediately after left hemithyroidectomy, loss of hyperesthesia and hyperalgesia with partial return of symptomatology 6 weeks postoperatively. Dots indicate regions of hyperesthesia; solid black areas indicate regions of local bone tenderness.

Observations on the early relief of pain in the patients presented in Table 1, and the sudden loss of hyperesthesia and hyperalgesia in patients M. G., M. S. and R. S., resembled the findings of others following cervical sympathectomy or paravertebral alcohol injection for relief of pain in angina pectoris.<sup>40, 43, 50, 55</sup> In patients with bilateral angina pectoris it has been observed<sup>54</sup> that unilateral cervical sympathectomy usually results in freedom from pain only on the operated side. If the early relief of pain after total thyroidectomy were due to interruption of nerve pathways, it was felt that after hemithyroidectomy patients might likewise show a unilateral loss of the pain of angina pectoris on the operated side. Three patients were studied in whom only one lobe of the thyroid was removed. Two-stage operations were indicated in these patients for reasons which will be outlined in forthcoming communications. Pre-operatively, each of the 3 patients showed accurately reproducible attacks of angina pectoris with pain referred to both sides of the chest and over the inner aspects of both arms.

*CASE 18.—Coronary sclerosis, bilateral angina pectoris. Loss of angina in right chest and arm after right hemithyroidectomy. Partial return of symptoms in 7 weeks. Loss of angina in left arm and chest after left hemithyroidectomy.* M. H., a male, aged 54, entered the hospital because of angina pectoris of 2 years' duration, due to arteriosclerotic heart disease. The attacks appeared only on exertion, with knifelike pain over the precordium, radiating to the sternum, right chest, both scapulae, inner aspects of both arms, the throat and both sides of the neck and face. (Fig. 4, a.) Characteristic attacks were precipitated regularly after 52 to 57 trips on the staircase under the standard conditions described elsewhere. The basal metabolic rate before operation was  $\pm 5\%$ .

At operation (October 16, 1933), only the entire right lobe of the thyroid was removed. The next day the patient spontaneously stated that for the first time in many months the right chest felt "free of pain and oppression." The left chest still felt "heavy and filled with discomfort." Two weeks after operation, the basal metabolic rate was unchanged, and attacks of angina pectoris were precipitated by exercise (57 trips on the staircase). The patient was surprised, however, that in contrast to the pre-operative bilateral distribution of the crushing pain he had always experienced, after right hemithyroidectomy no pain was experienced in the right chest, shoulder and neck. Pain was experienced only in the left chest, shoulder and arm, and terminated sharply at the midline of the chest. (Fig. 4, b.) During the next 4 weeks after discharge, the patient reported that attacks of angina, precipitated by walking in the street, were felt only in the left chest and arm. From the 5th to the 7th week, the patient noticed a gradual extension of pain to the right chest and shoulder and a return of pressure on the right chest during attacks of angina.

Seven weeks postoperatively, while walking, the patient developed an attack of angina pectoris, which gave rise to pain on the right as well as on the left side of the chest, anteriorly and posteriorly. It was similar in severity to those experienced before right hemithyroidectomy. The sense of oppression over the right chest returned, though definitely decreased compared to its intensity before operation. These characteristics of the spontaneous attacks were corroborated by similar attacks reproduced after 52 trips on the staircase under standard conditions. On January 8, 1933, left hemithyroidectomy was performed. On the same day of operation

the patient noted the absence of precordial pain which had been present pre-operatively and was not associated with exertion. Two weeks after operation the patient made 84 trips on the staircase without developing pain in the chest or arms. After exercise was over, a sense of pressure developed in both sides of the chest. The basal metabolic rate at this time was  $-4\%$ .

CASE 19.—*Coronary thrombosis, bilateral angina. Loss of angina in left arm and chest after left hemithyroidectomy. Return of symptoms in 21 days.*

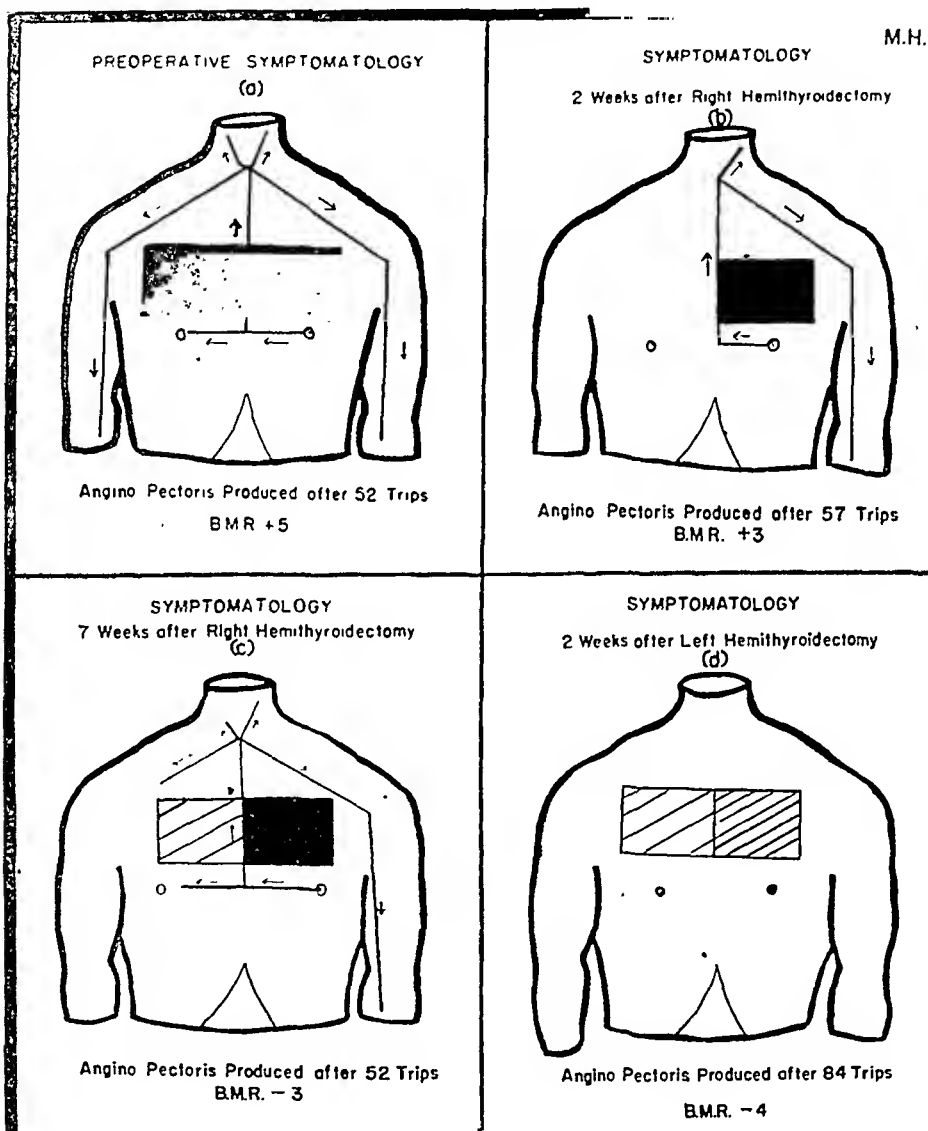


FIG. 4.—Case 18. After right hemithyroidectomy, loss of pain and oppression of angina pectoris experienced in right chest and arm. Return of symptoms 7 weeks after operation. After left hemithyroidectomy, complete loss of anginal pain and diminution in oppression. Lines indicate radiation of pain; blackened areas indicate oppression; hatched areas indicate diminution in oppression.

S. F., a male, aged 53, entered the hospital with the diagnoses of healed coronary thrombosis and angina pectoris. For 2 years walking a block always gave rise to crushing substernal pain, radiating to both chests, to the jaw, down both arms and to both scapulae. The pain always lasted 5 to 15 minutes and was regularly accompanied by an intense choking and

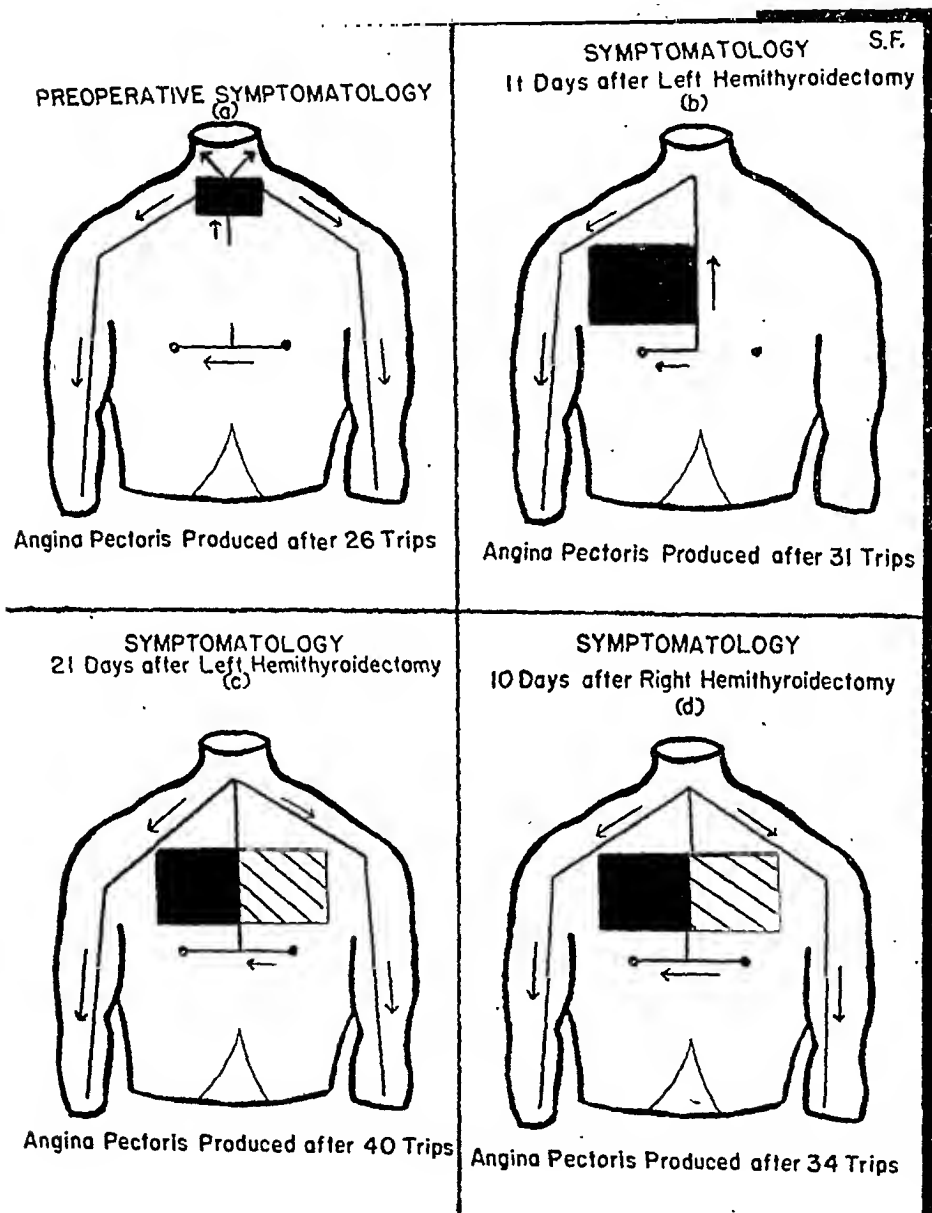


FIG. 5.—Case 19. After left hemithyroidectomy, loss of pain and oppression in right chest and arm. Twenty-one days after operation, return of symptoms. No changes in symptoms immediately after right hemithyroidectomy. Lines indicate radiation of pain; blackened areas indicate oppression; hatched areas indicate diminution in oppression.

gripping sensation over the throat. These attacks could be precipitated by exercise in the cold (31 trips on the staircase). (Fig. 5, *a*.) On November 7, 1933, a left hemithyroidectomy was performed. Five days later the patient experienced a characteristic attack of angina pectoris while at complete rest, except that for the first time in 2 years no pain whatsoever was referable to the left arm or chest. During the 2d postoperative week, similar attacks occurred, precipitated by exercise in the cold (31 trips on the staircase) (Fig. 5, *b*), no discomfort being experienced over the left

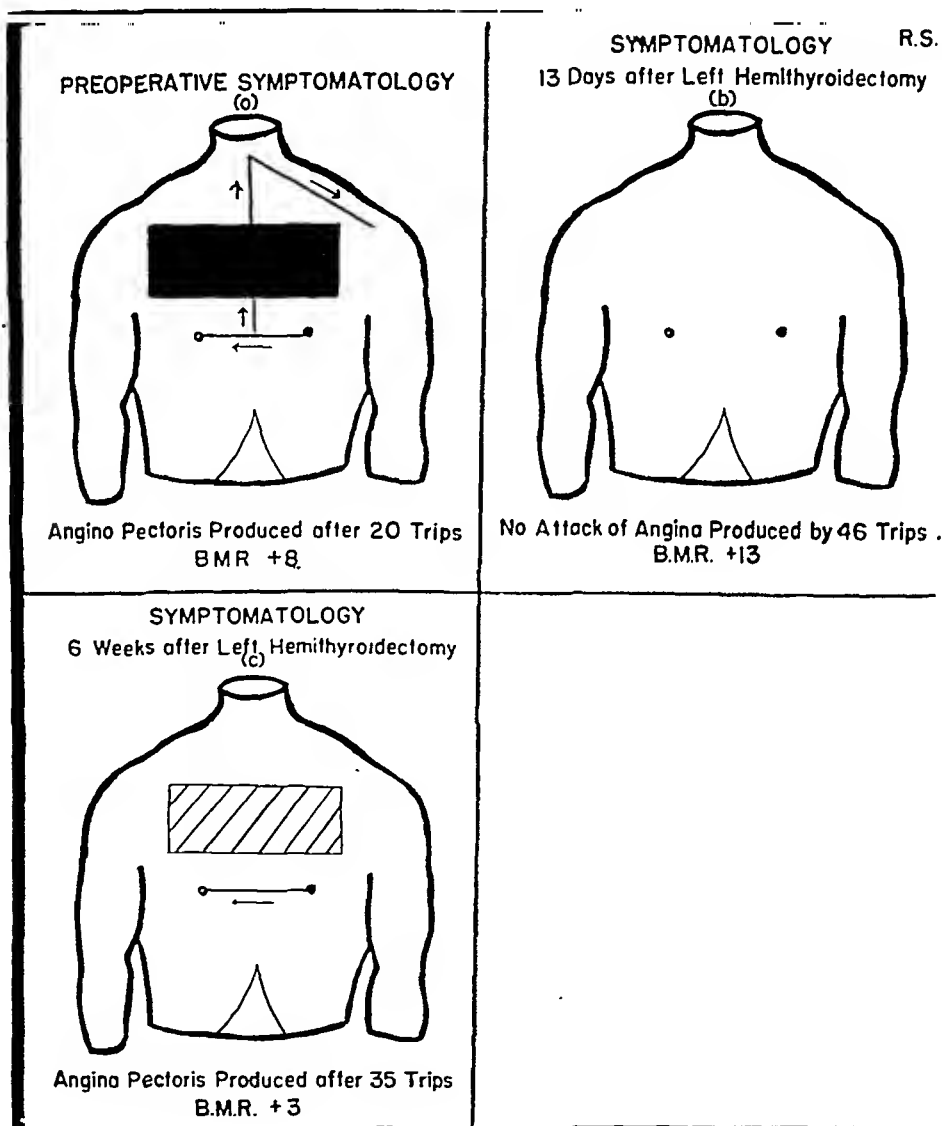


FIG. 6.—Case 20. After left hemithyroidectomy, complete loss of angina pectoris, with partial return of symptoms 6 weeks after operation. Lines indicate radiation of pain; blackened areas indicate oppression; hatched areas indicate diminution in oppression.

chest or arm. At no time before or after operation could satisfactory basal metabolic readings be obtained, in spite of many determinations.

During the 3d postoperative week the pain referable to the left chest gradually returned when attacks occurred spontaneously or under standard conditions. (Fig. 5, c.) The sense of oppression was less intense. At the beginning of the 4th postoperative week, the right lobe of the thyroid was completely removed. Ten days after the second lobe of the thyroid had been removed, attacks of angina pectoris were produced on exercise (34 trips on the staircase), pain being experienced over both chests, anteriorly and posteriorly, accompanied by numbness and pain in both arms. (Fig. 5, d.) The "heavy, choking and gripping feeling" in the throat was absent, however.

CASE 20.—(Same as Case 17.) *Coronary thrombosis, angina pectoris. Loss of angina pectoris after left hemithyroidectomy. Return of symptoms in 6 weeks.* R. S., a male, aged 41, who was admitted with the diagnoses of mitral stenosis and regurgitation, aortic insufficiency, coronary thrombosis and angina pectoris, had attacks of angina which were precipitated by slight exertion but occasionally awakened him at night. The attacks were characterized by "crushing" pain under the xyphoid, with "choking" sensations in the neck and radiation of pain to the left shoulder, left back, left arm and occasionally to the right arm. A "bandlike" sense of constriction in the right and left 3d interspaces was always present during the attacks. In addition to these attacks, he had suffered from a continuous sense of "pressure and stabbing pain" over the precordium, which was aggravated by eating, going to stool, or excitement. These attacks could be precipitated by exercise in the cold (20 trips on the staircase). The distribution of pain at this time is illustrated by Fig. 6, a.

The left lobe of the thyroid was completely removed, November 28, 1933, under local novocain anesthesia. Two hours after operation the sense of "tightness" across the left chest had disappeared, as had the sharp "stabbing" pains about the left nipple. Ten hours postoperatively the findings were corroborated, no sedation having been given in the meantime. Thirteen days after operation, on exercise under standard conditions (46 trips), no attack of angina was produced. (Fig. 6, b.) The basal metabolic rate was +13%.

Six weeks after left hemithyroidectomy, after 35 trips on the staircase, a mild attack of angina was experienced. (Fig. 6, c.)

In brief, after hemithyroidectomy, attacks of angina pectoris pain were not experienced over the side of the chest corresponding to that on which the thyroid had been removed. In 2 patients, M. H. and S. F., attacks of angina pectoris were precipitated as readily as before operation, the pain being confined to the half of the thorax corresponding to the intact lobe of the thyroid. All patients showed immediate postoperative relief on the operated side of non-anginal precordial pain which had been continuously present before operation. The basal metabolic rate showed no lowering after hemithyroidectomy, and within 3 to 6 weeks pain was again experienced as before operation.

The data in this communication on the immediate postoperative relief of pain are representative of a larger series of similar observations.

*Discussion. The early relief of chest pain after complete removal of the thyroid is due to interruption of nerve impulses and is temporary.*



We believe that the foregoing observations constitute convincing evidence that the early relief of pain after total ablation of the thyroid is due to the interruption of nerve pathways bearing afferent impulses from the heart to the central nervous system. This evidence may be summarized as follows:

1. *The loss of hyperesthesia and hyperalgesia of the chest and the subjective relief of precordial pain occurred immediately after operation.* After operations under local novocain anesthesia, the patients were examined and questioned within a few hours. The immediate loss of precordial pain and the sudden disappearance of certain localized areas of hyperesthesia and hyperalgesia could not have been due to diminished circulating thyroid principle within the body, for, even a week after operation, the basal metabolic rate often was only slightly lowered. The immediate postoperative relief was not due to local novocain infiltration for similar findings were observed in patients after general nitrous oxide anesthesia.

2. *The areas of hyperesthesia and hyperalgesia and precordial pain not infrequently reappeared before any considerable reduction in the metabolic rate occurred.* Recurrence of precordial pain occurred at various time intervals and was either partial or complete in intensity. The areas of hyperesthesia and hyperalgesia usually recurred in 3 to 6 weeks. The recurrence of symptoms presumably was due to resumption of function of nerves temporarily rendered non-conductive, to regeneration of nerves, or to other nerves taking over the function of the severed ones. Painful afferent nerve impulses from one source may not be appreciated because of greater cord stimulation from another source, such as the operative incision, the sensation from the latter source taking precedence over the former.<sup>52</sup> This counterirritant mechanism of relief of pain does not apply to our cases, for, although the operative incision was bilateral, the relief of pain was limited to the side on which hemithyroidectomy was performed. Moreover, the relief of pain frequently continued after the operative wound had healed.

3. *The unilateral relief of pain, typical of angina pectoris, by hemithyroidectomy constitutes striking evidence of the interruption of afferent impulses from the heart.* In each of the 3 patients with bilateral distribution of anginal pain, the attacks were not experienced over the side of the chest corresponding to that on which the thyroid had been removed. The characteristics of the attacks of angina pectoris, so far as they were referred to the unoperated side of the chest, were usually uninfluenced by operation. These findings in the 3 patients who had complete removal of only 1 lobe of the thyroid are plainly inconsistent with possible theories based on generalized changes of a metabolic or endocrine nature.

4. *The early relief of pain after thyroidectomy is closely analogous to the early effects of cervical sympathectomy.* Both hemithyroidectomy and unilateral cervical sympathectomy are attended by

somewhat irregular therapeutie effects. The relief is usually confined to the side of operation; recurrence of symptoms may be partial or complete and not infrequently occurs after an interval of days or weeks. Other changes were noted following thyroideectomy which indicate sympathetic nerve injury or stimulation; dilatation of 1 pupil was present for several days after operation in 2 patients; in 3 others, paresthesias of the neck, head and chest occurred, lasting 1 to 3 weeks. We have observed, moreover, that injection of the stellate ganglion with novocain causes temporary relief of hyperesthesia and hyperalgesia on the homolateral side of the chest.

The present status of knowledge regarding the anatomy and pathologic physiology of the cervical sympathetic nerves does not permit us to state the exact pathways that suffer interruption. "Viscrosensory" or "viscromotor reflex arcs" may be affected.<sup>35</sup> Impulses from the heart reach the central nervous system directly through the thoracic sensory nerves and also by way of sensory fibers traveling the same pathway as the cervical sympathetic fibers.<sup>54</sup> The relative importance of these 2 routes evidently varies from person to person, thereby accounting for the great variability in therapeutie results of cervical sympathectomy as well as the variability of the early relief of pain found by us following thyroideectomy in different individuals. Complete surgical removal of the thyroid probably does not involve severance of the main cervical sympathetic trunk or ganglia or of the cardiac nerves in the neck, although some of the numerous ramifications of this system, such as the plexuses along the inferior and superior thyroid arteries, may suffer interruption.

*The early relief of pain is not due to decrease in sensitivity of the heart to epinephrin or other endocrine substances.* As pointed out in a previous communication,<sup>12</sup> the heart in patients with angina pectoris may be less sensitive to epinephrin when the basal metabolic rate is lowered following total thyroideectomy. This assumption is based on experimental observations that the effect of epinephrin on the heart may be enhanced in man and animals receiving thyroid active principle, and, conversely, may be diminished in patients with myxedema.<sup>1, 15, 21, 32, 36, 42</sup> These findings, based on blood pressure and heart rate measurements, have received clinical application in the "Goetsch test."<sup>24</sup> Experience has shown, however, that the sensitivity of the heart to epinephrin is far too irregular both in normal man and in patients with thyroid disease to be an index of the degree of thyroid activity.<sup>14, 46, 51</sup>

The early relief of pain following thyroidectomy, as described above, is not associated with a significant reduction in the amount of circulating thyroid active principle. That the relief in these patients during this period can be due neither to reduction in the basal metabolic rate nor to decreased sensitivity of the heart to epinephrin is, therefore, obvious. Our own observations of the effect of epinephrin in such patients are in accord with this con-

sideration. This concept is further substantiated by the fact that patients in whom hemithyroidectomy was performed experienced unilateral relief of pain on the operated side. Mechanisms based on early general metabolic or endocrine influences, moreover, cannot explain the temporary return of precordial pain which frequently occurs several weeks after total ablation of the thyroid, and before the basal metabolic rate has dropped appreciably.

*The permanent relief of pain occurs later in the postoperative course with the development of the hypothyroid state as gauged by the basal metabolic rate.* The foregoing observations reaffirm the importance of the lessened work of the heart, when the metabolic rate becomes lowered, as the basis for permanent improvement in patients with angina pectoris or congestive failure. Earlier measurements of the velocity of blood flow in various clinical conditions indicated that the work of the heart was greatly decreased in myxedema and that a damaged heart, while unable to supply the demands of the body at normal metabolic rates, might nevertheless be able to supply the lowered tissue demands after complete thyroidectomy.<sup>8</sup> In accord with these considerations we have found that the signs of circulatory insufficiency lessen most markedly as the amount of circulating thyroid principle, as gauged by the metabolic rate, diminishes, and that the degree of permanent improvement in patients with congestive failure or angina pectoris is closely related to the extent of the lowering in the basal metabolic rate. As Means stated, 1924, in his monograph on dyspnea, "First of all comes treatment directed toward reduction of the metabolic rate. This is seen most strikingly in treatment by rest, particularly in heart failure."<sup>37</sup> In patients with low pre-operative basal metabolic rates, the improvement has not been as striking as in patients with normal pre-operative metabolic rates in whom the postoperative decrease was greater.

According to current knowledge, the outstanding function of the thyroid is to regulate the general level of metabolic activity, with important effects also on the nervous system and on growth.<sup>39</sup> The chief expenditures of cardiac energy are in relation to cardiac output and velocity, ventricular rate and blood pressure.<sup>5, 10</sup> Studies on which we are engaged indicate that these various factors all play a part, but that the reduction in the cardiac output and velocity is most important in releasing the heart from strain; the reduction in ventricular rate is of secondary importance and changes in the blood pressure are negligible.

Changes in supply and demand also contribute to the benefits conferred to patients with angina pectoris.<sup>7-10, 38</sup> At rest, the coronary circulation is evidently adequate to the needs of the heart muscle, as evidenced by freedom from pain. During exercise, however, as a result of organic lesions such as arteriosclerotic narrowing of the coronary vessels, the coronary blood supply cannot increase in accord with the increased needs of the heart, and so pain ensues.<sup>28, 38, 49</sup>

Following permanent reduction in the basal metabolic rate by thyroidectomy, there is marked reduction in the work demanded of the heart, as gauged by the velocity of blood flow and cardiac output.<sup>4, 10, 13</sup> During exercise the demands of the heart for oxygen and nutrition rise. Since the heart in the hypothyroid state is starting at a lower level of oxygen consumption than in the normal state, it can withstand a greater increment of work before reaching the upper limit of oxygen supply set by the relatively fixed coronary vessels. The rôle of this factor is being investigated.

Another benefit conferred by thyroidectomy on the hearts of patients with chronic heart disease may be the total decreased expenditure of cardiac energy associated with the lowered total metabolism of hypothyroidism.<sup>20</sup> The value of bed rest in patients with angina pectoris has long been recognized by clinicians. The reduction in total metabolism toward the basal rate which accompanies bed rest greatly diminishes the work of the heart<sup>20</sup> and is associated with clinical improvement. This is in accord with the findings of other observers that conditions which increase the work of the heart precipitate attacks of angina<sup>16-18, 45, 48</sup> and, conversely, that treatment which reduces the burden on the heart alleviates angina pectoris.<sup>2, 25, 26, 31</sup>

Our experience has been in accord with these considerations. Of 20 patients with angina pectoris, all operated upon without mortality, 14 have been able to undertake various degrees of work; 4 are recently postoperative; the 2 who received only slight relief had low basal metabolic rates prior to operation and consequently showed no great further reduction before thyroid extract had to be administered to prevent myxedema.

*The relation between the early relief of pain due to nerve impulse interruption and the later permanent relief of pain due to lowering of the metabolic rate.* According to current concepts, there are 3 ways in which referred visceral pain may be abolished: (1) Abolition of cutaneous afferent impulses; (2) interruption of the nerves carrying abnormally strong visceral afferent impulses; (3) altering the state of the viscus so that it no longer gives rise to abnormally strong impulses. The 1st mechanism, studied extensively in various diseases by Weiss and Davis,<sup>53</sup> plays no rôle in the relief of pain after thyroidectomy. The cutaneous nerves of the areas studied are not affected, for anesthesia of the skin was not demonstrable in our subjects, in contradistinction to the observations after novocain infiltration of Weiss and Davis. In patients with hemithyroidectomy, unilateral relief was experienced, although the skin incision was the same as for total thyroidectomy. The 2d mechanism is probably the basis of the early relief of pain experienced by our patients and may have either an anatomic or a physiologic basis. In some patients, practically all afferent impulses may be interrupted; in others a sufficient number of impulses may be blocked so that the remaining functioning fibers transmit stimuli which are only sub-

liminal. The 3d mechanism provides the later and permanent relief of pain by permanent reduction in the basal metabolic rate and the lessened demands on the heart.

It should be noted that the 2 mechanisms which we regard as providing relief of pain are independent in their action and occur at different times postoperatively.

After total thyroidectomy, in some patients the metabolic rate became lower while the early relief of pain was present. In these patients, therefore, the relief of pain was continuous. (Fig. 7, *c*.) In other patients, however, the pain due to nerve impulse interruption recurred, only to disappear permanently when the basal metabolic rate showed a marked reduction. (Fig. 7, *b*.) In other patients there may be no early relief of pain. (Fig. 7, *a*.) Obviously various combinations of these two variable mechanisms produce a variable clinical course in any given patient.

The observation of unilateral relief of pain after hemithyroidectomy raises considerations of practical importance. The underlying pathologic disorder was evidently unaffected, for the attacks of anginal pain on the other side of the chest were usually precipitated as readily and as intensely as previously. The abrupt cessation of attacks sometimes witnessed immediately after bilateral removal of the gland may, therefore, be due to interruption of impulses from the heart to the central nervous system without reflecting any fundamental improvement in the heart itself. The unilateral relief of angina pectoris immediately after hemithyroidectomy is strong evidence that early bilateral relief after total thyroidectomy is due to the same mechanism. Such patients may simply be unaware of attacks during their early convalescence after total ablation of the thyroid and, by undertaking exertion too soon, may jeopardize their well-being. The advisability of enforcing complete bed rest in such patients, as well as in all others, until the basal metabolic rate shows significant lowering is apparent.

**Summary and Conclusions.** 1. Observations on the immediate postoperative relief of chest pain after total thyroidectomy in 19 patients are described.

2. Data were collected before, immediately after and during several weeks after operation in 3 groups: (1) Changes in non-anginal precordial pain; (2) changes in areas of skin hyperesthesia and muscle and periosteal hyperalgesia of the chest wall; (3) changes in the character and distribution of pain of angina pectoris.

3. Within a few hours after operation, non-anginal precordial pain, hyperalgesia and hyperesthesia disappeared, remained absent for 2 to 4 weeks, but then usually reappeared if the basal metabolic rate had not declined significantly. Only after the basal metabolic rate had dropped appreciably did the above-mentioned signs and symptoms diminish or disappear permanently.

4. Studies were made on the distribution of the pain of angina pectoris produced under standard conditions in 3 patients before

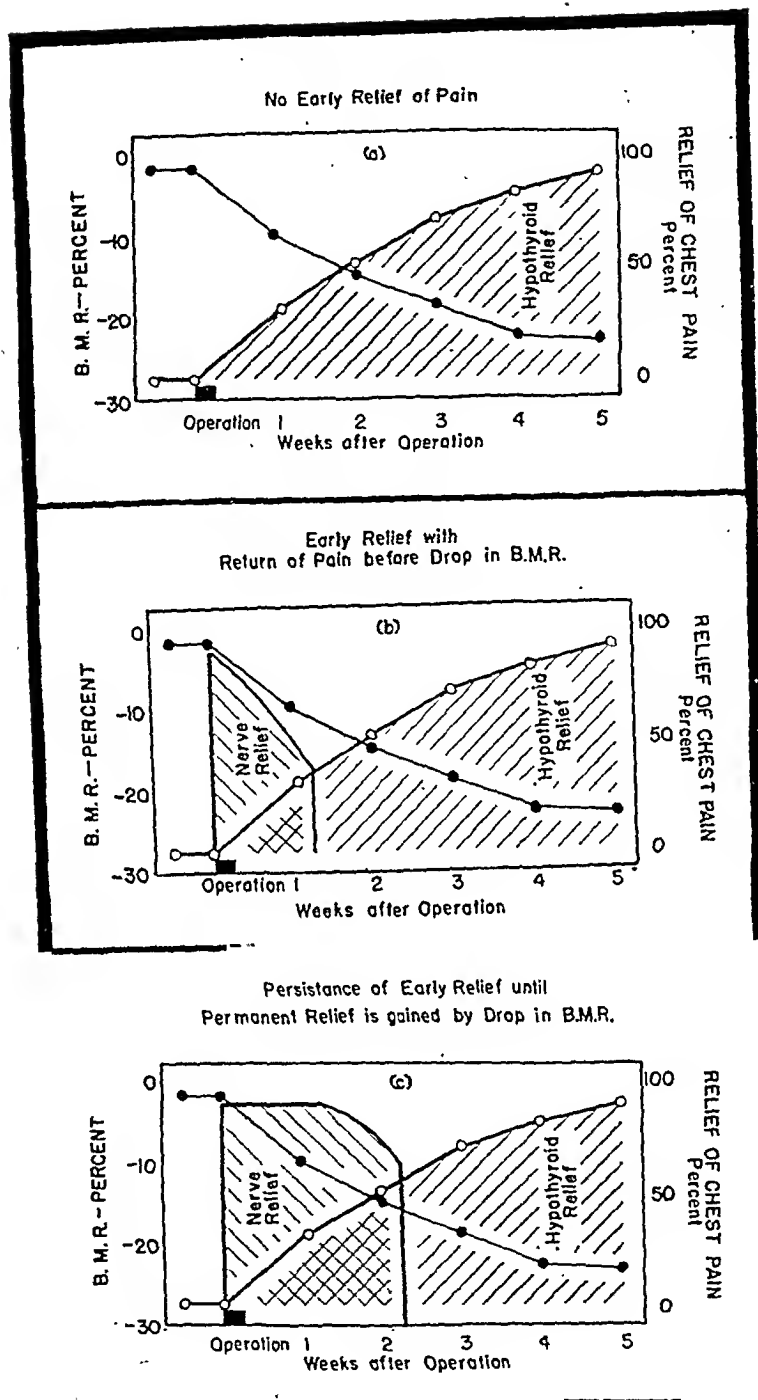


FIG. 7.—Possible variations in the clinical picture of relief of chest pain and angina pectoris following total thyroidectomy. The hatched area, on the left of chart, bounded by the solid black line indicates early relief of pain due to nerve injury; the hatched area, on the right of the chart, bounded by the line broken by circles indicates the development of permanent relief of pain due to the development of the hypothyroid state. The cross-hatched area indicates overlapping of these two mechanisms. The basal metabolic rate lines represent actual average values taken from the postoperative course of 25 patients after total ablation of the thyroid. The curve after subtotal thyroidectomy in patients with toxic goiter is somewhat different according to the work of Segall and Means.<sup>47</sup>

and after hemithyroidectomy. The remaining half of the thyroid gland was removed at a later date. Exercise within 2 weeks after hemithyroidectomy produced no pain in the arm and the side of the chest corresponding to the side of operation. The pain of angina pectoris was experienced only on the unoperated side and usually stopped sharply at the midline of the sternum. The similarity of these findings to those after cervical sympathectomy and alcohol injection is disscussed. The basal metabolic rate did not change appreciably after the 1st hemithyroidectomy. After 2 to 8 weeks, pain on exercise was again experienced on the operated side. Only after removal of the other  $\frac{1}{2}$  of the thyroid gland and after an appreciable drop in the basal metabolic rate was the pain of angina pectoris permanently relieved.

5. These observations point definitely to the following conclusions: (1) The immediate relief of pain after total thyroidectomy is due to the interruption of afferent nerve impulses from the heart at the time of operation; (2) relief by this mechanism is only temporary; (3) permanent relief is related to the lessened work of the heart attendant on the development of the hypothyroid state.

6. These findings indicate that, after total ablation of the thyroid, complete bed rest should be enforced, despite the early subjective relief experienced by the patient, until the basal metabolic rate shows significant lowering.

We wish to thank Dr. James C. White for his helpful suggestions.

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## RHEUMATIC HEART DISEASE: CLINICAL DATA AS OBSERVED IN LOUISVILLE, KENTUCKY.\*

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In the present study a 5-year survey of rheumatic heart disease in a charity hospital in Kentucky (L. C. H.) is offered. The purpose of this investigation is to ascertain the incidence and course of

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rheumatic heart disease in this section and to compare the data in this group of cases with similar groups reported in the literature from other sections of the United States.

There were admitted to the wards of this hospital during the 5-year period of this study (1928-1933) 206 proven cases of rheumatic heart disease being 8% of the total admission of cardiac cases.

**Race and Sex.** In this group there were 84 males (41%) and 122 females (59%). This shows the usual more frequent incidence of the rheumatic infection in females in the ratio of 3 to 2. The racial incidence was 130 whites (63%) and 76 colored (37%) (Table 1).

TABLE 1.—RACE AND SEX INCIDENCE (COMPLETE GROUP).

	Sex.			Race.	
	Cases.	%		Cases.	%
Males . . .	84	41	White . . .	130	63
Females . . .	122	59	Colored . . .	76	37
Total . . .	206	100	Total . . .	206	100

**Etiology.** Of this series 140 cases (68%) gave a definite history of mild or severe rheumatic fever; 40 (19.4%) had only recurrent attacks of tonsillitis; and 9 (4.3%) gave a history of chorea. Seventeen (8.2%) gave no history of previous illness that could be interpreted as a rheumatic infection. The sexes were almost equal in the chorea group and were in the ratio of 2 to 3 in the rheumatic fever and tonsillitis group (Table 2).

TABLE 2.—ETIOLOGY OF COMPLETE GROUP.

	Cases.	%	Sex.	
			Males.	Females.
Rheumatic fever . . . . .	140	68.0	55	85
Chorea . . . . .	9	4.3	4	5
Tonsillitis . . . . .	40	19.4	13	27
No history . . . . .	17	8.2	7	10
Total . . . . .	206	100.0	79	127

In the group of 140 cases giving a history of rheumatic fever, it is interesting that only 2 developed the infection before 5 years of age. The first rheumatic attack was before the age of 20 in 98 cases (70%) and 131 (93.5%) were stricken before the age of 30.

TABLE 3.—THE INCIDENCE OF RHEUMATIC FEVER BY DECADES.

Decades.	Cases.	%
0 to 10 years . . . . .	28	20.0
10 to 20 years . . . . .	70	50.0
20 to 30 years . . . . .	33	23.5
30 to 40 years . . . . .	8	5.7
40 to 50 years . . . . .	1	0.8

**Onset of Symptoms.** At some time during the 5-year period covered by this study 155 cases of the whole group were admitted

with cardiac symptoms (Table 4). There was a progressive increase in the number showing symptoms with each decade to the age of 40. The greatest number showed cardiac symptoms between the second and fifth decades (58%). Nine cases did not develop symptoms until after the 50th year. Fifty-one cases were in the hospital for other conditions and signs of rheumatic heart disease were unexpectedly discovered.

TABLE 4.—ONSET OF CARDIAC SYMPTOMS (155 CASES).

Decade.	Cases.	%
0 to 10 . . . . .	6	4
10 to 20 . . . . .	35	22
20 to 30 . . . . .	40	26
30 to 40 . . . . .	50	32
40 to 50 . . . . .	15	10
50 or over . . . . .	9	6
Total . . . . .	155	100

**Clinical Diagnosis.** The whole group classified according to the clinical diagnosis of valvular involvement shows: (1) Mitral, 160 cases; (2) aortic, 11 cases; (3) mitral and aortic, 22 cases, and (4) auricular fibrillation, 13 cases. In 21 cases of the group a diagnosis of mitral stenosis and auricular fibrillation was made clinically. Therefore, in the entire group auricular fibrillation was present clinically in 34 cases. Mitral valve involvement alone was present in 83%, aortic lesions alone in 5.7% and both mitral and aortic involvement in 11.3%.

TABLE 5.—CLINICAL DIAGNOSIS OF VALVULAR LESIONS (193 CASES).

Valve.	Cases.	%
Mitral . . . . .	160	83.0
Aortic . . . . .	11	5.7
Aortic and mitral . . . . .	22	11.3
Total . . . . .	193	100.0

**Deaths.** To permit comparative study, the cases in which death occurred in the hospital have been divided into two groups: (1) fatal cases not autopsied, 25; and (2) fatal cases autopsied, 11.

**Discussion.** GROUP 1. (Fatal cases without autopsy.) This group is comprised of 25 cases and shows a definite dominance of females, 11 members of the group being males and 14 females, a ratio of 4 to 5 (Table 6). Sixteen cases gave a history of rheumatic fever, 7 gave a history of tonsillitis, and 2 no history of a rheumatic infection. The initial attack of rheumatic fever occurred before the 30th year in every case except one (96%). The greatest incidence occurred in the 2d decade, 9 cases (56%). The greatest number of this group had onset of cardiac symptoms in the 3d decade of life, and in only 3 cases were symptoms delayed until after 50. Mitral stenosis was diagnosed in 12 cases, mitral and aortic lesions in 5, mitral stenosis and auricular fibrillation in 5, and auricu-

TABLE 6.—FATAL CASES (NO AUTOPSY).

Case No.	Age.	Sex.		Rheu. fever.	Tonsillitis.	Chorea.	Age.	Onset of symptoms.	Death.	Valve lesion.	Cause of death (clinical).
		Male.	Female.								
1	22		F.	+			22	32	32	Mitral	Congestive failure.
2	19		F.		+			21	24	Aur. fibrillation	Congestive failure.
3*	34		F.					32	34	Aur. fibrillation	Congestive failure.
4	24	M.		+			15	24	25	Mitral.	Congestive failure.
5	40		F.	+	+			40	40	Mitral	Congestive failure.
6	32		F.	+			10	31	33	Mitral	Congestive failure.
7	33	M.		+	+			21	33	Mitral	Sub. bacterial endocarditis.
8	51		F.		+			50	51	Mitral	Pericardial effusion.
9	44		F.	+			23	42	48	Mitral; aur. fibrillation	Congestive failure.
10	49		F.	+			6	47	49	Mitral; aur. fibrillation	Congestive failure.
11	46		F.	+			35	46	46	Mitral	Congestive failure.
12	37		F.		+			33	37	Mitral; aur. fibrillation	Congestive failure.
13	55	M.		+			17	52	55	Mitral	Congestive failure.
14*	22	M.						20	22	Mitral; aur. fibrillation	Congestive failure.
15	45		F.	+			10	32	35	Mitral	Congestive failure.
16	31	M.		+			20	31	31	Mitral and aortic	Congestive failure.
17	32		F.	+			28	31	34	Aur. fibrillation	Congestive failure.
18	31	M.			+			30	31	Mitral and aortic	Congestive failure.
19	32	M.		+			20	30	32	Mitral and aortic	Pneumonia.
20	37	M.		+			24	24	37	Mitral	Congestive failure.
21	52	M.		+			12	52	52	Mitral and aortic	Congestive failure.
22	44	M.			+			35	44	Mitral; aur. fibrillation	Congestive failure.
23	26		F.	+			12	22	29	Mitral	Congestive failure.
24	42		F.	+			18	34	45	Mitral and aortic	Congestive failure.
25	31	M.		+			14	31	31	Mitral	Congestive failure.
Totals and average		11	14	16	7	0	18	34	38	25	25

\* No history of rheumatic infection.

TABLE 7.—FATAL CASES (AUTOPSED).

Case No.	Age.	Sex.		Rheu. fever.	Tonsillitis.	Chorea.	Age.	Onset of symptoms.	Death.	Cause of death.
		Male.	Female.							
1	22	M.			+			2	21	Mitral stenosis. Positive blood culture. Followed scarlet fever. Death due to septicemia.
2	39		F.	+			16	39	39	Mitral stenosis. No symptoms. Death due to ruptured uterus.
3	51		F.	+			24	51	53	Mitral stenosis. Infarct left lung. Coronary sclerosis. Congestive failure.
4	31	M.		+			14	31	31	Vegetative endocarditis. Mitral stenosis. Congestive failure.
5	36	M.		+			36	36	36	Aortic and mitral stenosis. Postoperative death from ruptured duodenal ulcer.
6	18		F.	+			13	17	19	Mitral stenosis. Congestive failure.
7*	42		F.					42	42	Generalized valvulitis. Congestive failure. All valves incompetent.
8	45		F.			+	6	26	27	Mitral stenosis. Infarct both lungs. Congestive failure.
9*	40	M.						39	40	Mitral stenosis. Coronary sclerosis. Congestive failure.
10*	19	M.						19	19	Mitral stenosis. Vegetative endocarditis. Congestive failure.
11	10	M.		+			9	11	13	Mitral stenosis. Congestive failure.
Totals and averages	32	6	5	6	1	1	17	27	30	

\* No history of rheumatic infection.

lar fibrillation alone in 3 cases. The average age at death in the whole group was 38 years. The average age at death in the cases of pure mitral stenosis was 35; in the cases of mitral and aortic lesions, 38; mitral stenosis and auricular fibrillation, 40; and in the cases showing only auricular fibrillation the average age at death was 30 years. The cause of death based on clinical diagnosis was congestive failure in 22 cases (88%). Subacute bacterial endocarditis, pneumonia, and pericarditis with effusion were responsible for 1 death each.

**GROUP 2. (Deaths, autopsied.)** This group is comprised of 11 cases, 6 males and 5 females. As to etiology, 6 cases gave a history of rheumatic fever, 1 a history of tonsillitis, 1 had chorea and 3 gave no history of rheumatic infection. The average time elapsing from the first attack of rheumatic infection to the onset of symptoms was 10 years. The average time from onset of symptoms to death was 3 years. The cause of death was congestive failure in 8 cases. One died from a ruptured uterus, 1 from septicemia following scarlet fever, and 1 from a ruptured duodenal ulcer (postoperative). Nine cases of this group showed mitral stenosis, 1 showed both aortic and mitral stenosis and in 1 all valves were incompetent.

**Comparison of Findings with Other Sections of the United States.** It is interesting to note the incidence of rheumatic heart disease in the Louisville City Hospital is practically the same as reported from Texas by Stone and Vanzant (1927), and is in close agreement with statistics submitted by Harrison and Levine (1924) from a charity hospital in New Orleans. It serves to emphasize the effect of climate in the incidence of the rheumatic state. This study would indicate that, in general, White's conclusions with reference to this point may be accepted. In other words, in the southern United States the rheumatic infection occurs about  $\frac{1}{4}$  as often as in New England and about  $\frac{1}{2}$  as often as in Virginia and Maryland. Throughout, the infection is essentially one of youth and early adult life. In general, the infection behaves the same in all latitudes, producing the same characteristic endocardial lesions, and possibly invading the walls of the larger bloodvessels with resulting fibrosis and scars. The predominating lesion in groups reported from different communities is mitral stenosis. The victims generally must lead sheltered lives and death overtakes them in the third and fourth decades of life. The most usual cause of death is congestive failure in all series reported from that standpoint.

**Summary.** In this study of 206 cases of rheumatic heart disease seen in the Louisville City Hospital, it was revealed that 84% were less than 50 years of age. The disease occurred most commonly in the 3d and 4th decades of life (58%). Only 9 patients (6%) were more than 50. The sex incidence showed the usual greater frequency of the infection in females in the ratio of 3 to 2. There was a predominance of white patients to colored in the ratio of 5 to 3. There

was a definite history of rheumatic infection in 189 cases (91%). One hundred and forty cases (68%) had rheumatic fever. The first attack occurred before the age of 30 years in 131 cases (93.5%) and before the age of 20 in 98 cases (70%). The primary infection occurred in only 1 case after the age of 40.

One hundred and fifty-five cases were in the hospital some time during the period covered by this study with cardiac symptoms (75%). The greatest number developed symptoms during the 3d and 4th decades of life, and 131 cases (85%) had shown some degree of decompensation before the 40th year. Only 9 cases were over 50 when symptoms appeared.

For the purpose of comparative study the fatal cases in this series were divided into two groups according to autopsy or no autopsy examination. Group 1, in which no autopsy examination was made, comprised 25 cases, and Group 2, in which an autopsy examination was made; 11 cases. In Group 1, 11 patients were males and 14 were females; the rheumatic infection occurred before the 30th year in every case except 1. The average age at death was 36 years. In Group 2 there were 6 males and 5 females; the rheumatic infection occurred before the 30th year in every case except 1; and the average age at death was 30 years. At autopsy 9 cases showed mitral stenosis, 1 mitral and aortic stenosis, and 1 showed incompetency of all valves. Death was due to congestive failure in 30 of the 36 fatal cases. One died of a ruptured uterus, 1 of a ruptured duodenal ulcer (postoperative), 1 of septicemia, 1 of pneumonia, 1 of pericarditis with effusion, and 1 of subacute bacterial endocarditis.

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### THE CLINICAL SIGNIFICANCE OF LOW T-WAVES IN THE ELECTROCARDIOGRAM.

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ALTHOUGH the clinical significance of inverted *T*-waves in one or more leads of the electrocardiogram has been studied extensively, little information is available concerning upright *T*-waves of small amplitude. In 1924, Pardee<sup>1</sup> stated that a *T*-wave less than 2 mm.

in amplitude in the lead showing the largest excursion should probably be considered abnormal. Master<sup>2</sup> believes that low voltage *T*-waves not exceeding 1 mm. amplitude in any lead furnish significant evidence of cardiac damage. The present study is concerned with *T*-waves less than 2 mm. in amplitude in Leads I and/or II. The electrocardiograms have been classified as follows: (A) Low *T*-wave in Lead I and normal *T*-wave in Lead II. (B) Low *T*-waves in Leads I and II and either low or slightly inverted *T*-wave in Lead III. (C) Normal *T*-wave in Lead I, low or flat *T*-wave in Lead II and inverted *T*-wave in Lead III.

Some of the tracings of Type B are similar to those published by Master, although in many the *T*-waves are greater than 1 mm. in amplitude, in one or more leads.

The clinical material used in the study has been divided into the following groups:

(1) 709 college students with presumably normal cardiovascular systems; (2) 23 cases having a "vertical" heart; (3) 25 pregnant women; (4) 202 cases showing a low *T*-wave (less than 2 mm.) in Lead I or II or both; (5) 100 cases with normal electrocardiograms; (6) 143 cases with hypertension; (7) 145 railroad executives.

GROUP I. The records of 709 college students with presumably normal cardiovascular systems were made available by Dr. Francis C. Wood. There were 46 cases whose *T*-waves conformed to one or another of the types under consideration; 34 to Type A; 7 to Type B, and 5 to Type C.

Analysis of the records showing a low *T*-1 suggested a relationship between this wave and the *Q*-*R*-*S* complex of Lead I. In 32 the amplitude of the *Q*-*R*-*S* complexes was 6 mm.\* or less and in 23, 4 mm. or less. It would, therefore, appear that in young individuals with apparently normal hearts, a low *T*-wave in Lead I is encountered in less than 5% of the cases and in most of these the *Q*-*R*-*S* complex is also of low amplitude. However, the converse is not true, for *T*-waves of normal amplitude are frequently found associated in Lead I with low *Q*-*R*-*S* complexes.

Orthodiagrams were available in only 9 of the 32 cases showing a low *T*-1, but it was noteworthy that 7 of the 9 showed a "vertical" heart.

Examination of the 7 records with a low *T*-1 and *T*-2 showed *Q*-*R*-*S*-1 complexes of less than 6 mm. in 4 instances. Orthodiagrams were available in 3 of the 4 cases showing a low *Q*-*R*-*S*-1, and in 2 the heart was of the vertical type. The *Q*-*R*-*S* complexes of the remaining 3 cases were split or slurred in all leads. Follow-up studies of these individuals have not been obtained and the significance of the finding is not known.

Further examination of the 5 electrocardiograms showing a normal *T*-1, low *T*-2 and inverted *T*-3 revealed nothing else of note. Ortho-

\* Throughout this paper an *R*-1 of 6 mm. amplitude or less will be considered as low.

diagrams were available in 3 cases and in each the left diaphragm was on the level of the right; in 2 cases the heart appeared transversely placed.

GROUP II. The frequency of vertical hearts in young individuals with low  $T$ -1 waves suggested that position of the heart may be an important factor in producing the low  $T$ -1. Low  $Q$ - $R$ - $S$  complexes in Lead I have frequently been noted in electrocardiograms of patients whose hearts were of the vertical type,<sup>1</sup> and, as is well known, in cases with a tendency toward right axis deviation, particularly mitral stenosis. In order to obtain some idea regarding the frequency of low  $T$ -1 waves in cases with vertical hearts, a group of orthodiagrams exhibiting such hearts was selected at random from the orthodiagraphic files. Only those orthodiagrams exhibiting a normal-sized heart were chosen; records suggesting a "mitralized" heart were not included. The clinical histories and electrocardiograms of these cases were then studied and those with evident cardiovascular disease excluded. Twenty-three cases remained and in 17 the  $R$ -waves in Lead I were 6 mm. or less in amplitude; in 7 records,  $T$ -1 was less than 2 mm. A low  $T$ -1 was associated with a low  $R$ -1 in 6 cases. It would therefore appear that in patients with vertical hearts, a low  $Q$ - $R$ - $S$  complex is obtained in the majority in Lead I. Furthermore, the low  $Q$ - $R$ - $S$  complex frequently has associated with it a low  $T$ -1.

GROUP III. The position of the heart also affects the  $T$ -waves in Leads II and III. Bland and White<sup>3</sup> have noted a complete inversion of Lead III in transversely placed hearts and Proger<sup>4</sup> has shown that  $T$ -3 is inverted in a large percentage of obese individuals with apparently normal hearts. In order to study the influence of a high diaphragm upon  $T$ -3, the electrocardiograms of 25 pregnant women (9th month) were examined. In 22,  $T$ -3 was inverted, in 2 it was flat and in only 1 was it upright. Although there are factors other than a high diaphragm which may influence the form of the electrocardiogram during pregnancy, it was noteworthy that in 10 cases examined after delivery,  $T$ -3 which had been inverted became upright or flat in 9 and in only 1 was there no change. Although the  $T$ -wave in Lead II was of low amplitude in only 3 of the 25 cases, in each of these 3 cases  $T$ -3 was inverted; following delivery,  $T$ -2 became of normal amplitude and  $T$ -3 upright. In all cases the  $T$ -wave in Lead I was of normal amplitude and in 13 cases 4 mm. or more. Of the 10 cases examined after delivery, 9 showed a reduction in amplitude of  $T$ -1; although this reduction was slight in some cases, nevertheless in 4 instances it was 2 mm. or more.

GROUP IV. In order to correlate the clinical and electrocardiographic findings in cases whose electrocardiograms showed a low  $T$ -wave in one or more leads the records of 202 clinic and ward patients were studied. This group was divided as follows:

Type A, 68 cases; Type B, 80; Type C, 54.

A. Among these 68 cases, the clinical records disclosed cardiovascular abnormalities in 57 (83.8%); 3 cases (4.4%) were considered doubtful because their complaints or findings pointed to cardiac damage but sufficient evidence was not found to warrant a definite diagnosis; in 8 (11.8%) there was no evidence of cardiovascular abnormality. Although 22 tracings showed a low *R*-1, in 5 cases there was mitral stenosis and right axis deviation; in 2, mitral stenosis without right axis deviation. In only 2 instances was there a vertical heart without evidence of organic disease.\* All of the remaining 13 cases showed some cardiac abnormality. The association of low *T*-1 and *R*-1, as found in Groups I and IV, therefore, may be due either to vertical position of the heart or to myocardial change, the incidence of each depending on the type of clinical material being studied.

The clinical diagnosis of those cases showing a cardiovascular abnormality are as follows: Hypertension and/or arteriosclerosis (including 3 cases of angina pectoris), 23; rheumatic heart disease, 10; myocardial disease (etiology unknown), 7; thyrotoxicosis, 6; syphilitic heart disease, 5; miscellaneous, 6.†

B. In this group there were 80 cases. The clinical records of 70 (87.5%) disclosed cardiovascular abnormalities; in 2 (2.5%) the diagnosis was doubtful, and 8 (10%) were negative. The clinical diagnoses of the positive cases are: Hypertension and/or arteriosclerosis (including 2 cases of angina pectoris), 24; rheumatic heart disease, 12; myocardial disease (etiology unknown), 14; thyrotoxicosis, 10; syphilitic heart disease, 5; miscellaneous, 5.

C. In this group there were 54 cases and, of these, 34 (63%) disclosed cardiovascular abnormalities, 2 (3.7%) were doubtful, and 18 (33.3%) were negative. The clinical diagnoses of those cases considered positive are: hypertension and/or arteriosclerosis, 13; rheumatic heart disease, 6; myocardial disease (etiology unknown), 3; thyrotoxicosis, 5; syphilitic heart disease, 4; miscellaneous, 3.

The chief significant difference elicited among the 3 types appeared to be the somewhat higher percentage of cases with negative or doubtful clinical findings in Type C.‡ It is worthy of note that in 6 of the 20 cases falling in this category (Type C) the heart was transversely tilted by a high diaphragm.

GROUP V. The clinical histories of 100 ward and clinic patients whose electrocardiograms were considered normal were studied. This group was considered essential as a control group and the

\* There were only 2 cases of hypertension in the group of 22 showing a low *R*-1. The association of a normal or large *R*-1 and a low *T*-1 is apparently much more frequent in such cases.

† Under "miscellaneous" are grouped such conditions as congenital heart disease, acute and subacute bacterial endocarditis, acute pericarditis, pleuropericarditis, metastatic carcinoma and severe cases of kyphoscoliosis.

‡ Thirty-two (15.8%) of the 202 cases showed slurring or splintering of the *Q*-*R*-*S* complexes in one or more leads; 15 belong to the group considered under Type A, 10 to Type B and 7 to Type C.



cases were chosen at random from electrocardiographic files. Forty-one of this group were considered as having positive evidence of cardiovascular abnormality, 9 were doubtful and 50 were considered negative. The clinical diagnoses of those cases considered positive are: hypertension and/or arteriosclerosis (including 1 case of angina pectoris), 16; rheumatic heart disease, 12; myocardial disease (etiology unknown), 1; thyrotoxicosis, 4; syphilitic heart disease, 5; miscellaneous, 3.

The negative group consisted of a great variety of conditions. Although the patients in this group were derived from the same sources as those of Group IV, the different incidence of cardiovascular disease is striking. This finding points strongly to the significance of low *T*-waves.

GROUP VI. This group consists of 145 corporation executives. They are of importance in this study because of the frequency of arteriosclerosis and hypertensive cardiovascular disease in this group. All were referred for routine examination and all were on the active list of this corporation at the time of examination although 1 had had a coronary occlusion.

A. There were 20 records with a low *T*-wave in Lead I. Clinically, 10 were considered as having a cardiovascular abnormality. Of the remainder the low *T*-wave was associated with a low *R* in 7 instances; in 5 of these 7 the heart was vertical. It was smaller than normal in 3 of these 5. Of the 3 remaining cases, focal infection (teeth and tonsils) was stressed in the clinical records of 2; the third was considered negative.

B. There were 4 records showing a low *T*-1 and *T*-2. The electrocardiogram of 1, a man of 32, showed a low *R*-1. Clinically nothing but a few abscessed teeth were found. The other 3 disclosed findings indicative of cardiovascular damage.

C. There were 2 cases with a low *T*-2 and inverted *T*-3. One showed a slight increase in width of the aorta on fluoroscopic examination but was otherwise negative. Nothing of significance was found on examination of the other.

GROUP VII. Because of the great number of cases of hypertension showing a low *T*-wave in important leads (Group IV), a group of 143 cases of hypertension was studied. Only those patients with systolic blood pressure consistently above 150 mm. or diastolic pressure consistently over 100 mm. are included. Master,<sup>5</sup> in his study of hypertensive hearts, found left axis deviation in 74% and left axis deviation with inversion of *T*-1 in 36% of cases. In our group of 143 cases left axis deviation was found in 95 (66.4%); in 59 cases (41.3%) the *T*-wave was diphasic or inverted in Leads I or II or both. In 30 instances (21%) the *T*-waves corresponded to one of the types under consideration in this study, 15 to Type A, 12 to Type B and 3 to Type C. The much greater incidence of these types in hypertension than in normal controls constitutes evidence

of their significance. It is also of interest that only 3 of the group of 30 cases with low *T*-waves showed a low *R*-1.

**Discussion.** Variations in the angle of the electrical axis of the heart in the normal individual is an important factor in determining the height and form of the components of the electrocardiograms. Although intrathoracic conditions are frequently responsible for changes in the anatomical axis of the normal heart and presumably also of the electrical axis, the position of the diaphragm is probably the most frequent factor.

That a low *T*-wave in Lead I is frequently dependent on a low position of the diaphragm is supported by several observations: (1) The frequency of low *T*-1 in the group of vertical hearts; (2) in tracings taken during inspiration and expiration, *R*-1 and *T*-1 frequently tend to become smaller during inspiration; (3) following pregnancy the *T*-wave in Lead I became smaller in the majority of cases.

The view that a high diaphragm tends toward an inversion of *T*-3 is supported by the following: (1) The frequency of inverted *T*-3 in electrocardiograms of pregnant women and their reversion to an upright *T*-wave after delivery; (2) the frequency of inversion of *T*-3 in obese individuals; (3) the changes in *T*-3 during a deep expiration.

It therefore appears that in properly evaluating the significance of a low *T*-1 or *T*-2 in doubtful cases, cognizance must be taken of the position of the heart; in vertical hearts without evidence of disease, *T*-1 may be low or flat but is usually associated with a low *R*-1, and in obese individuals an inverted *T*-3 is often present and is sometimes associated with a low or flat *T*-2.

The relative incidence of myocardial damage or of position of the heart as a cause of low *T*-waves depends on the type of material being studied. The high percentage of cases with low *T*-wave, showing evidence of cardiovascular disease from ward and clinic sources might be interpreted as indicating that small *T*-waves are to be regarded as strong evidence of cardiac damage.\* If, on the other hand, one's observations were limited to a group of presumably well individuals, the inference might be drawn that the chief cause of low *T*-waves is abnormal position of the heart.

The problem might, however, be considerably simplified from the standpoint of electrocardiographic interpretation if it were not for a group of cases in which there is no evidence either of myocardial damage or abnormal position of the heart. In our Group IV it would appear that a number of cases fall in such a category although the actual percentage is small. There are several possible explanations for such cases: (1) Myocardial changes may be present but

\* The assumption that low *T*-waves found in cases showing cardiac disease are necessarily due to myocardial damage cannot be established. Thus, it is possible that in mitral stenosis the frequent finding of a low *T*-1 is more often dependent on altered position of the heart than on damage of the myocardium.

not recognized clinically;\* (2) there may be enough rotation of the heart, without definite assumption of a vertical or horizontal position, to modify the *T*-waves;† (3) small *T*-waves may occur independently of myocardial abnormality or altered position of the heart.

**Summary.** 1. A vertical or transverse position of the heart has a marked influence upon the ventricular waves of the electrocardiogram. In vertically placed hearts *R*-1 is frequently low and often a low *T*-1 is associated. In transversely placed hearts *T*-3 is very frequently inverted and is sometimes associated with a low *T*-2; in many cases these findings are also associated with left axis deviation.

2. Although the association of low *T*-1 and *R*-1 is frequently encountered in vertical hearts it is also found in the presence of cardiovascular damage, especially in rheumatic heart disease.

3. The association of a low *T*-1 and high *R*-1 is usually encountered in cases showing some cardiovascular abnormality, especially hypertension. It has, however, been observed in a few cases in which no cardiovascular abnormality was demonstrable.

4. The incidence of definite cardiovascular abnormality found in cases referred from wards and out-patient clinics for electrocardiographic study which could be classified in one or another of the electrocardiographic types under consideration was as follows: Type A (Low *T*-1 and normal *T*-2) 83%; Type B (low *T*-1 and *T*-2) 87%; Type C (normal *T*-1, low or flat *T*-2 and inverted *T*-3) 63%. In cases derived from the same sources but with normal electrocardiograms, the incidence of definite cardiovascular abnormality found was 41%.

5. The percentages obtained for the incidence of myocardial damage or position of the heart as the cause of the low *T*-waves of the type classified under A and C depends mainly on the type of material being studied. In groups of presumably normal individuals, position is the more important; in groups suspected of heart disease, myocardial damage is the more important. In certain cases with heart disease, however, the *T*-wave changes may be due to altered position of the heart rather than myocardial damage *per se*. We have obtained no evidence to indicate that small *T*-waves in all leads may be dependent on position of the heart.

6. Roentgen ray study of the heart is essential in attempting to evaluate the significance of low or flat *T*-waves in either Lead I or Lead II of the electrocardiogram.

7. For guidance in the clinical interpretation of electrocardiograms we believe the following statements are justified:

A. An electrocardiogram with a low *R*-1 and low *T*-1 and a

\* The not infrequent association of severe illness with small *T*-waves in all leads suggests that in such cases the myocardium may have suffered from the effects of the illness. In a number of such cases followed for months up to a year or more after recovery, the electrocardiogram has returned to normal. A normal electrocardiogram has been obtained in some cases soon after recovery.

† Certain electrocardiographic changes associated with the production of artificial pneumothorax support this view. (Unpublished observations, Edeiken and Lieberman.)

normal *T*-2 points either to abnormality of the heart or to vertical position. When the heart is vertically placed no significance can be ascribed to these findings as evidence of cardiac abnormality. When, however, the heart occupies its usual position, the low *R*-1 and *T*-1 suggest that it may be abnormal.

*B.* The association of a normal or high *R*-1 and a low *T*-1 offers strong but not certain evidence of cardiac abnormality.

*C.* The finding of small *T*-waves in all Leads is probably rarely if ever dependent on position of the heart. It furnishes strong presumptive evidence of abnormality of the heart.

*D.* The combination of a normal *T*-1, a low or flat *T*-2 and an inverted *T*-3 may be due either to abnormality of the heart or to a more transverse position than is usual. When the heart is transversely placed, such an electrocardiogram may not be regarded as evidence of myocardial abnormality; when, however, the heart occupies the usual position, such a tracing suggests myocardial abnormality.

*E.* It is possible that in a small minority of cases, these various types of electrocardiograms may occur in the absence both of altered position of the heart and abnormality of the myocardium.

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### THE ELECTROCARDIOGRAM IN ACUTE EXPERIMENTAL DISTENTION OF THE RIGHT HEART.\*†

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THESE experiments were carried out to determine whether significant electrical deviations accompany acutely developed distention on one side of the heart. A long time, often a number of years, is required for the development of a marked shift in the

\* Aided by the Emil and Fanny Wedeles Fund of the Michael Reese Hospital for the Study of Diseases of the Heart and Circulation.

† This report is the completion of a study begun by one of us (W. C. B.).

electrical axis in the human heart, although very rapid shifts occur that are not easily accounted for except on the basis of a change in the heart's position.

Several types of experiments were performed. In the first group of experiments, 15 adult unanesthetized dogs, weighing between 7 and 26 kg., were used. In each, 5 cc. of metallic mercury were injected into a leg vein, and the hind leg was then elevated to facilitate the passage of the mercury to the heart. Metallic mercury was used because the obstructive effects of the metal following its widespread dissemination into the arterial side of the pulmonary circuit should lead to an acute right-sided distention. Its fluidity would avoid contact trauma. Electrocardiograms (standard leads) were obtained in the right and left lateral decubitus positions, before, shortly after and, provided the animal survived, 24 and 48 hours after the injection. In 10 animals the leads were taken in succession, in 5 they were recorded simultaneously (Leads I and II) by two electrocardiographs. The electrical axes were determined only on those curves satisfying with only slight error Einthoven's formula ( $E^1 = E^2 + E^3$ ). The distribution of the metal and the heart size were determined by fluoroscopy and Roentgen ray examinations. Autopsies were done on all animals and the weight and mercury content of the hearts determined. Three other animals were used (which were sacrificed within 10 minutes after mercury injection) to determine the acuteness with which the changes occurred in the thoracic viscera.

In a second group of experiments, 4 dogs anesthetized with morphin and barbital were used. The chest was opened and artificial respiration instituted. The effect of mercury injections on the pressure curves of the two ventricles was determined by optical recording with Wiggers' manometers simultaneously with the taking of the electrocardiograms. In these animals the effect of almost complete occlusion of the pulmonary artery by clamp was determined on the electrocardiogram and intraventricular pressure curves.

**Results.** The results in the first group of animals are summarized in Table 1. It will be seen that the average survival period of the 15 animals was 35 hours following the injection of mercury, and ranged from 5 to 102 hours. Symptoms were scarcely noticeable for 15 or 30 minutes, sometimes an hour or more after the injection. Dyspnea was absent or, if present, was very slight. Fluoroscopy at this time, however, revealed a fairly widespread dissemination of the metal even into the smaller pulmonary radicles (Fig. 1). The first symptoms that usually appeared were gastro-intestinal, with retching and vomiting. Nearly all of the animals were observed to defecate within an hour after the injection. In a few animals there was marked muscular collapse and prostration. Six or more hours after the injection, dyspnea became marked, there was cough and grunting respiration, nasal discharge and later cyanosis of the mucous membranes. The animals ate and drank very little.



FIG. 1.—Roentgen ray of chest (24 hours after a 5 cc. metallic mercury injection), showing widespread distribution of mercury in pulmonary vessels. Note the mercury in the right auricle and ventricle.



FIG. 2.—Microscopic appearance of myocardium following mercury injection. Note the very marked hyperemia.



FIG. 3.—Roentgen ray of heart removed post-mortem, showing the distribution of mercury in the right auricle and ventricle.

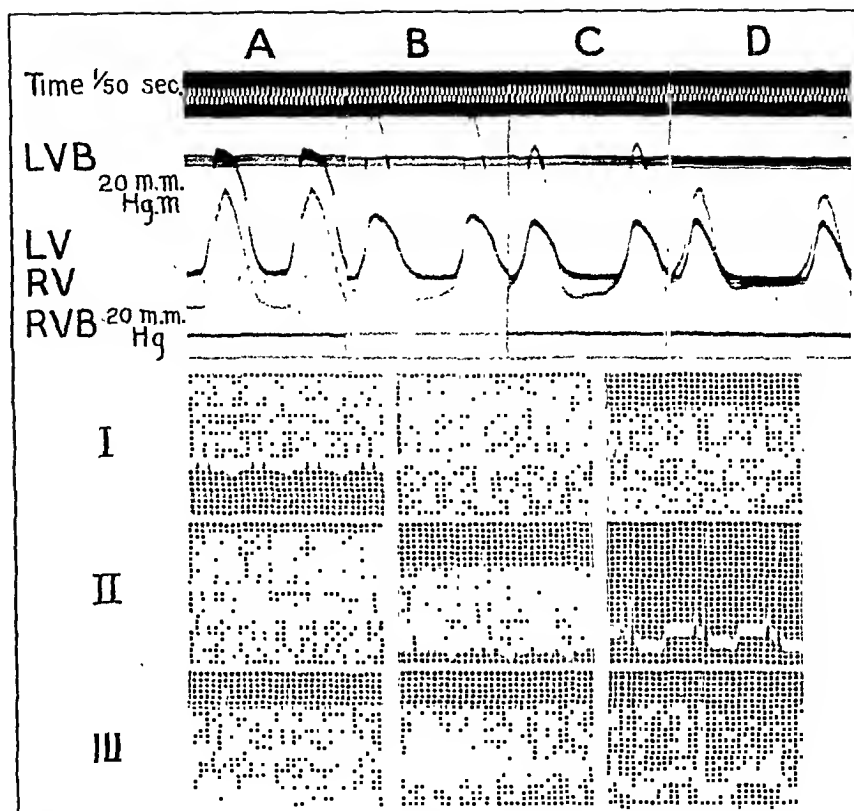


FIG. 4.—Simultaneous intraventricular pressure curves and electrocardiograms, showing effect of almost complete compression of the pulmonary artery. The intraventricular curves were recorded on a separate camera and are reduced to one-quarter their original size. The electrocardiograms are three-quarters natural size. Segment A is the control taken before compression, but some time after mercury injection. (This explains the relatively large systolic pressure in the right ventricle.) Segments B, C and D were taken 5, 10 and 30 minutes after compression of pulmonary artery. LV is the pressure curve of the left ventricle and LVB its base line. RV is the pressure curve of the right ventricle and RVB its base line. I, II, III are Leads I, II and III, respectively, of the electrocardiograms. No electrocardiograms were taken when Segment D was recorded. In Segments B, C and D, RV starts below LV, but crosses and goes above it during systole. The calibration of each pressure curve is given by the vertical line which represents the displacement caused by 20 mm. Hg. Note the appearance of a negative S-T in Segment C, which is probably due to the relative ischemia of the heart.

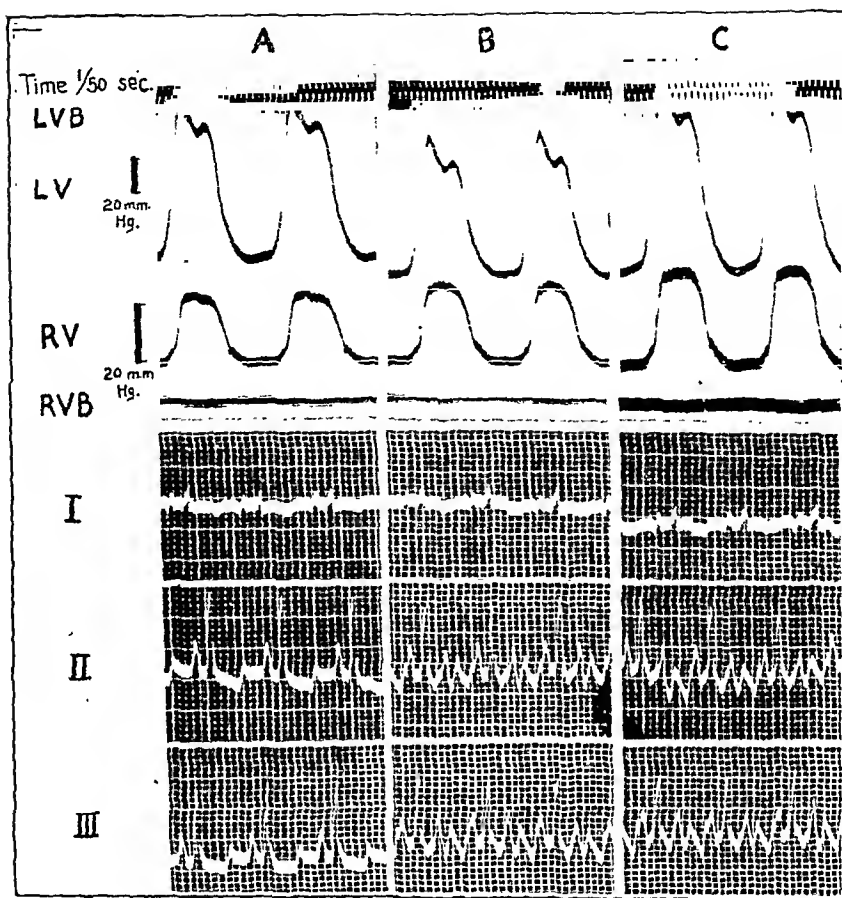


FIG. 5.—Simultaneous intraventricular pressure curves and electrocardiograms arranged as in Fig. 4, showing effect of mercury injection. Segment A is the control, Segments B and C were taken 1 and 5 minutes after mercury injection. Labeling and calibration as in Fig. 4.

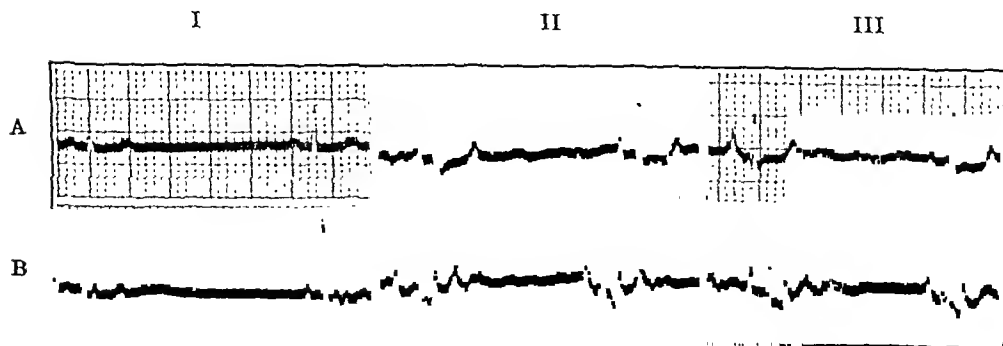


FIG. 6.—Electrocardiogram (standard leads) to show effect of mercury injections. Segment A control, B after mercury.



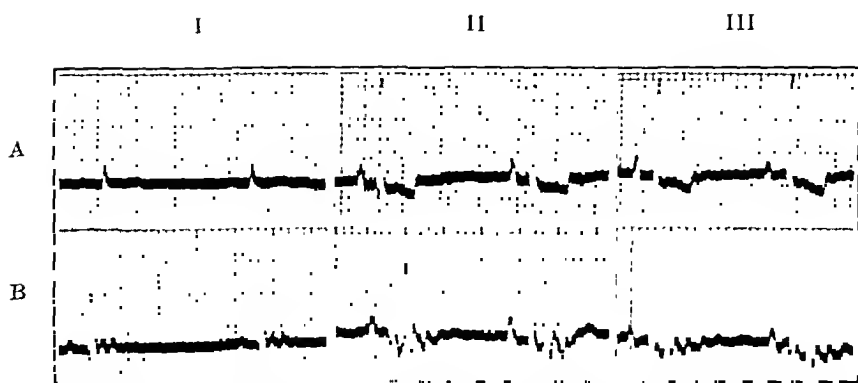


FIG. 7.—Electrocardiogram (standard leads) to show effect of mercury injections.  
Segment A control, B after mercury.

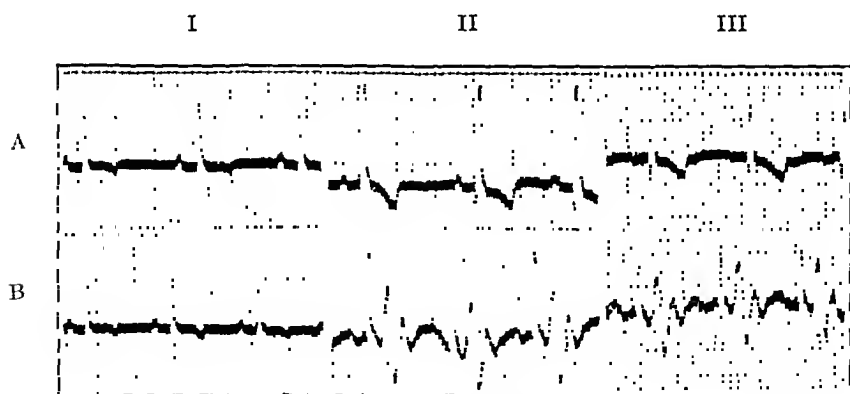


FIG. 8.—Electrocardiograms (standard leads) to show effect of mercury injections.  
Segment A control, B after mercury.

The essential changes at autopsy were, as expected, found in the thoracic viscera. There was marked dilatation of the right auricle and ventricle in all of the survival experiments. This was more prominent in those animals that survived a day or more. The left ventricle did not appear to be dilated. Small epicardial hemor-

TABLE 1.

Dog No.	Wt., kg.	Heart weight, gm.	Hg in right heart, gm.	Survival period, hrs.	Electrical axes.							
					Animal on right side.				Animal on left side.			
					Control, angle °.	5 to 10 min. after Hg, angle °.	24 hrs. after Hg, angle °.	48 hrs. after Hg, angle °.	Control, angle °.	5 to 10 min. after Hg, angle °.	24 hrs. after Hg, angle °.	48 hrs. after Hg, angle °.
1 . .	18.3	151.1	0.110	21	68	79	..	..	69	56		
2 . .	15.0	20.0	0.063	28	60	79	..	..	79	70		
3 . .	14.8	118.3	0.250	60								
4 . .	10.1	86.1	0.084	8	61	85	..	..	70	81		
5 . .	12.6	107.0	1.190	14								
6 . .	21.2	138.1	4.180	27								
7 . .	26.2	219.1	0.510	102	78	77	79	83	98	60	82	84
8 . .	21.0	131.1	0.033	68	69	79	66	..	79	66	78	
9 . .	9.7	101.1	0.710	5								
10 . .	19.6	136.2	2.810	18	54	49	..	..	77	69		
11 . .	9.9	84.7	0.022	29	*52	51	38	..	48	41	55	
12 . .	9.3	123.2	0.303	17	*56	51	..	..	72	42		
13 . .	15.7	148.2	0.207	62	*58	59	58	66	53	55	49	51
14 . .	7.3	72.0	0.042	48	*71	84	66	..	44	58	66	
15 . .	9.9	96.0	0.670	18	*60	71	..	..	57	53		
					<i>Animal Sacrificed.</i>							
16 . .	8.7	75.3	3.327	10 min. after injection.								
17 . .	8.9	69.1	0.390	8 min. after injection.								
18 . .	27.8	202.0	0.221	8 min. after injection.								

\* Leads I and II recorded simultaneously with two machines.

rhages occurred in the basal portions of the ventricles of several dogs in which the survival period was relatively long. No endocardial hemorrhages occurred. Microscopic sections disclosed intense hyperemia (Fig. 2). Although no epicardial or endocardial hemorrhages were noted in the hearts of the 3 animals used in the acute experiments, a microscopic section of portions of both right and left ventricles revealed marked capillary engorgement and diffuse intramuscular hemorrhage.

Formed thrombi containing mercury droplets filled the auricular appendages of more than  $\frac{1}{2}$  of the animals (Fig. 3). In several there were small mural thrombi in the ventricles. A small amount

of mercury in the superficial coronary veins\* was noted in 2 hearts. Approximately  $\frac{1}{4}$  of the mercury injected, or about 15 gm. ( $\frac{1}{6}$  or  $\frac{1}{8}$  of the entire weight of the heart) was recovered from the right chambers after death, least being found in those animals surviving longest. A little more than  $\frac{1}{3}$  of the injected mercury was recovered from the hearts of those animals immediately sacrificed. (The amount of mercury recovered from each heart, the weight of the heart and the survival period of the animal are given in Table 1.) There were a few mercury droplets of minute size, scarcely visible to the naked eye, in the left ventricles of 2 animals. The greater part of the mercury retained in the right auricle and ventricle was in the form of small droplets lodged in the recesses of the columnæ carneæ (Fig. 3). Larger accumulations seen in the apical portions of the heart may have been dislocated from the columnæ carneæ or from some pulmonary vessel.

The lungs were voluminous, wet and heavy, and usually did not collapse on opening the chest. They were the seat of infarctions. They were extensively mottled and colored purple, especially over the lower parts. There were extensive areas of consolidation throughout the lung fields. Several hundred cubic centimeters of a serosanguineous or fibrosanguineous fluid were present in the pleuræ of those animals that survived more than 24 hours; in 1 it was purulent. The lungs of the 3 animals immediately sacrificed appeared to be little less injured than those that survived many hours.

The changes noted in the other organs were essentially those of passive hyperemia and edema. The kidneys were not enlarged and the capsule stripped readily. There was no fluid in the pericardium and no inflammation about it.

*Heart Size and Distention.* Marked dilatation occurred regularly in the 5 animals that survived the injection of mercury for 24 hours. This was apparent on Roentgen ray examination and was found postmortem to involve the right heart. Dilatation was found in the other animals postmortem, even in the 3 sacrificed within 10 minutes of the injection of mercury. However, in the last animals the dilatation might have been agonal, especially in the animals where ether was used as the lethal agent. Roentgen rays of the dogs shortly after the injection of mercury failed to disclose any dilatation and, in the open-chested dogs, no dilatation was seen following mercury injection. It is, therefore, concluded that the dilatation of the right heart following mercury injection is a late phenomenon requiring a number of hours to develop.

In the open-chested animal experiments, tremendous right-sided dilatation at once followed the compression of the pulmonary artery. This procedure interfered so much with the output of the heart that the coronary flow was soon diminished and, as a conse-

\* This may have entered by a reversal of flow in these veins, such as Batson and Bellet<sup>2</sup> appear to have shown, or *via* the Thebesian channels as suggested by the work of Bohning, Jochim and Katz.<sup>3</sup>

quence, the dilatation shortly involved the entire heart. The stage of right-sided dilatation was distinct, however, and lasted an appreciable interval of time. This unilateral dilatation was accompanied by a rise in the diastolic pressure in the right ventricle and a greater increase in the systolic pressure (Fig. 4, Segments A and B). At the same time the diastolic and systolic pressure of the left ventricle fell. Later the pressures in the left ventricle continued to fall, while those in the right ventricle decreased also, to even below normal (Fig. 4, Segments C and D).

In the open-chested animal experiments, mercury injections caused an immediate and persistently increasing rise in the diastolic and systolic pressure of the right heart (Fig. 5) and a temporary fall in these pressures in the left ventricle. Presumably the same change occurred in the survival experiments in the first hour. The development of dilatation which occurred later in the survival experiments is due no doubt to weakening of the heart muscle by the action of the mercury.

*Electrocardiographic Changes.* Inspection of Table 1 and the electrocardiograms of Figs. 5 to 8 show that neither in the survival experiments nor in the acute open-chested animal experiments was there recorded any significant right axis deviation, even when there was marked dilatation of the heart.

Shortly after the injection of the metal in the animals which survived, a slight shift of the electrical axis to the right usually occurred when the animal lay on the right side, and a slight shift of about equal magnitude usually to the left occurred when the animal lay on the left side (Tables 1 and 2). The axis deviations at the end of 24 hours in the animals which survived were not significantly different from those found within 10 minutes after mercury injection. Considering the errors involved in measuring the angles and the theoretical inaccuracy of the concept of the Einthoven triangle, the changes are not of especial significance.

TABLE 2.—SHIFT IN ELECTRICAL AXIS BETWEEN CONTROL CURVES AND VARIOUS TIMES AFTER INJECTIONS OF MERCURY.

Animal No.	Animal on right side.			Animal on left side.		
	5 to 10 min., angle °.	Control and 24 hrs., angle °.	48 hrs., angle °.	5 to 10 min., angle °.	Control and 24 hrs., angle °.	48 hrs., angle °.
1	+11	..	..	-13		
2	+19	..	..	-9		
4	+24	..	..	+11		
7	-1	+1	+5	-38	-16	-14
8	+10	-3	..	-13	-1	
10	-5	..	..	-8		
11	-1	-14	..	-7	+7	
12	-5	..	..	-30		
13	-1	0	+8	+2	-4	-2
14	+13	-5	..	+14	+22	
15	+11	..	..	-4		

+ = shift in electrical axis to right.  
- = shift in electrical axis to left.

The electrical axis was found to differ in the control curves, depending on whether the animal lay on its right and left side, respectively (Tables 1 and 3). This difference in electrical axis

TABLE 3.—SHIFT IN ELECTRICAL AXIS WHEN ANIMAL MOVED FROM RIGHT TO LEFT.

Animal No.	Control, angle °.	After Hg injection.		
		5 to 10 min., angle °.	24 hrs., angle °.	48 hrs., angle °.
1 . . . . .	+ 1	-23		
2 . . . . .	+19	- 9		
4 . . . . .	+ 9	- 4		
7 . . . . .	+20	-17	+ 3	+ 1
8 . . . . .	+10	-13	+12	
10 . . . . .	+25	+20		
11 . . . . .	- 4	-10	+14	
12 . . . . .	+16	- 9		
13 . . . . .	- 5	- 4	- 9	-15
14 . . . . .	-27	-26	0	
15 . . . . .	- 3	-18		

+ = shift in electrical axis to right.

- = shift in electrical axis to left.

was slightly increased, as a rule, after the mercury was injected. This was no doubt due to the relatively heavy weight of the mercury ( $\frac{1}{3}$  to  $\frac{1}{6}$  the weight of the heart) within the heart. Some exceptions were noted and occasionally the difference was in the direction opposite to that anticipated. This confirms the observations of Meek and Wilson,<sup>4</sup> Nathanson,<sup>5</sup> and Katz and Ackerman,<sup>6</sup> who demonstrated that displacements of the heart around its antero-posterior axis either to the right or left do not always give the shift in electrical axis anticipated. Such anatomic rotations were prevented in the open-chest animal experiments by fixing the heart with the intraventricular manometers and a pericardial "cradle." The electrocardiographic curves in these experiments did not show any appreciable electrical axis shift, even with the extreme ballooning out of the right side of the heart which occurred following compression of the pulmonary artery (Fig. 4).

A rather characteristic aberration of the ventricular complexes was observed following the injection of mercury. During each systole of the heart, sharp notchings of short vibration period occurred. In some these were small in amplitude, resembling the distortions due to muscular tremor, except for the slower frequency (Fig. 7); in others they were larger and fewer in number, resembling diphasic extra *T* waves (Figs. 4, 5 and 6); and in still others they were so large as to resemble extra *Q-R-S* or *Q-R-S-T* complexes (Fig. 8).

**Comment.** There are no published data known to us in which the electrocardiographic effects of dilatation of the heart alone are clearly set forth. Herrmann and Wilson<sup>7</sup> have emphasized that shifts in the electrical axis seldom or never develop suddenly, and that the relative weight of the two ventricles may be one of many

factors which exert an influence on the electrical axis. This influence predominates only when the heart is greatly hypertrophied. The theory advanced by Fahr,<sup>8</sup> that shifts in the electrical axis may be produced by dilatation of one of the ventricles, has no experimental support. The results of Lundy and Woodruff,<sup>9</sup> that right and left axis deviation in the intact dog under ether anesthesia can be produced by distention of the respective ventricles, cannot be accepted as proof positive, as they themselves recognized. The electrical changes might have been produced by interference with the circulation of the heart itself or by possible effects of pressure on special structures within it. Some of these untoward features have been obviated in the experiments reported by us. However, in the animals which survived the injection, evidence of injury to both ventricles was found in the form of intense hyperemia and hemorrhage (Fig. 2).

The distortions of the ventricular complexes observed in these experiments are due to the short-circuiting effects of the mercury within the heart and lungs. They cannot be due to ventricular systoles, for they would have to occur while the ventricles are in the absolute refractory phase, obviously an impossibility. Furthermore, it can be shown that similar distortions can be produced by spraying the heart with mercury or by putting mercury into the pericardial sac (Jochim, Katz and Mayne<sup>10</sup>). It is unlikely that these short-circuitings may have altered the amplitude of the *Q-R-S* deflections unequally in the various leads, and so masked significant shifts of the electrical axis of the heart. In the experiments of Jochim, Katz and Mayne,<sup>10</sup> mentioned above, spraying the heart with mercury and placing mercury in the pericardium lead to no axis shift. Furthermore, it should be emphasized again that no axis shift occurred when the right-sided dilatation was produced by compression of the pulmonary artery.

**Summary.** 1. The production of diffuse pulmonary emboli of metallic mercury following its introduction directly into the right heart or systemic venous circulation causes acute distention of the right heart. In the more chronic experiments a marked degree of right-heart dilatation is regularly produced.

2. Instrumental compression of the pulmonary artery produces a marked ballooning out of the right side of the heart, followed soon after by a similar ballooning of the left side.

3. Acute distention or dilatation of the right heart in the above experiments is accompanied by no significant deviation of the electrical axis of the heart.

4. The peculiar aberration of the ventricular complex (*Q-R-S-T*) produced by mercury injection are illustrated, and evidence is presented to show that they arise because of short-circuits set up by the intracardiac and extracardiac metal.

The negative *S-T* segment following occlusion of the pulmonary artery (*cf.* Fig. 4) resembles the changes observed by Feil, Katz, Moore and Scott (*Am. Heart J.*, 1931, 6, 522) when the vena cava is occluded.

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## NOTE ON ELECTROCARDIOGRAPHIC CHANGES ACCOMPANYING ACUTELY INCREASED PRESSURE FOLLOWING PULMONARY ARTERY LIGATURE.\*

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CHANGES in the electrical axis of the ventricles (altered weight relations, shifts in position) have long been known to produce characteristic changes in the electrocardiogram. The electrocardiographic changes that follow sudden increase of intraventricular

\* Acceptance for publication of the preceding article in this number by Buchbinder and Katz recalled germane studies which had been made at Harvard in the summer of 1916, but, due to the disturbance in scientific work brought about by the World War, had never been completed. Inasmuch as there is apparently little published on the electrocardiographic effects of acute increase of intraventricular pressure, it would seem as if a short note might add to the evidence available on this problem. It is a pleasure to acknowledge, even at this late date, my debt to Dr. Alexander Forbes for his help, access to his string galvanometer and for the animals, many of which were used at the same time for his studies on the nerve impulse.

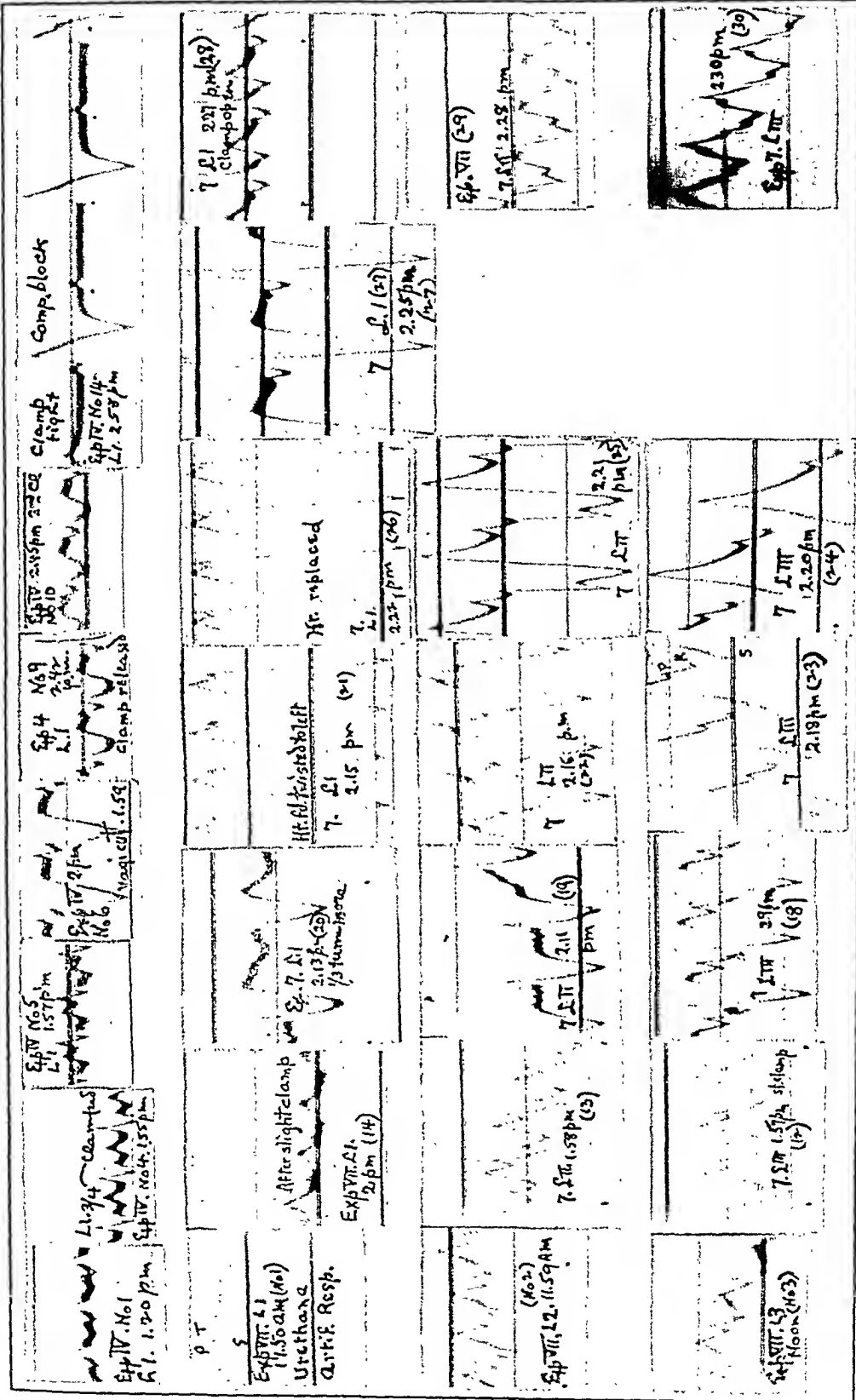
### LEGENDS FOR FIGS. 1, 2, 3 AND 4.

FIG. 1.—Exp. IV. Six records of Lead I only. Note change from an inverted to a prominent upright *P* wave, and the varying changes in the ventriculogram: diminution of *R* (No. 4), development of a slow *S* (No. 6), return of *R* on release of clamp (No. 9), finally complete *A-V* block with slow *R* and inverted *T* (No. 14). The *T* wave and the iso-electric period also show frequent changes. In this and subsequent records the string was standardized so that 1 M V = 2 cm. deflection (here reduced) and the film was run at the rate of 1 cm. per 0.01 second. Occasionally one complex in each strip has been retouched. The time marker has been omitted to save space.

FIG. 2.—Exp. VII. Note extreme development of *S*<sub>1</sub>, with obliteration of *T*<sub>1</sub>, disappearing on release of clamp (No. 28); development of *S*<sub>2</sub> and *S*<sub>3</sub> less marked; customary increase of *P* in all leads; in No. 27 marked slowing with extreme deflections; tendency for iso-electric period to disappear. In this and Fig. 4, to save time in shifting leads, records of Leads I, II and III were followed by the next set taken in reverse order (*i. e.*, Leads III, II, and I).

FIG. 3.—Exp. V. Four records of Lead II only. Note the increasing size of *P* in successive leads, also the change from a positive to a negative *T* (Nos. 2 and 11). In the final strip (dying heart) (No. 20), the rate is slow (*ca.* 45), all deflections are exaggerated and there is apparently an *A-V* rhythm.

FIG. 4.—Exp. VIII. Note numerous changes in *T* wave, also tendency for upstroke of *S*<sub>1</sub> (and downstroke of *R*<sub>3</sub>) to go beyond previous iso-electric level. In the last 6 records (Nos. 62-74), it appears as if a 2 to 1 *A-V* rhythm had been established.





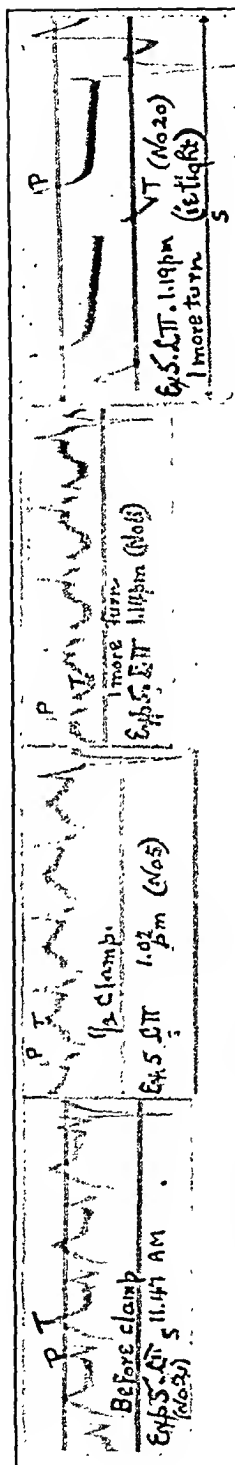


FIG. 3

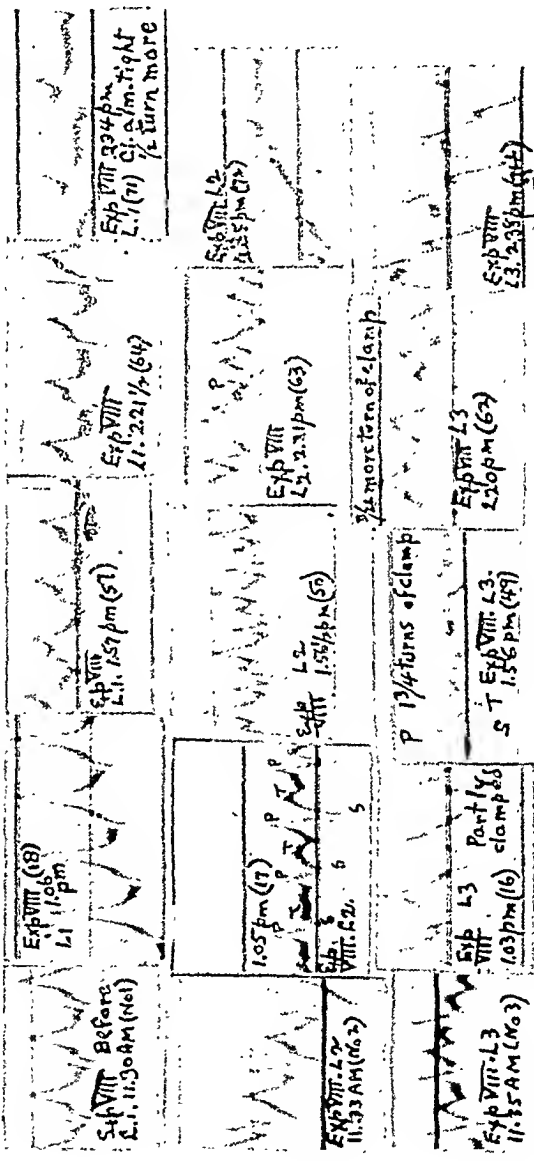


FIG. 4

pressure (before compensatory hypertrophy can occur) do not seem to have had equal attention (see preceding article):

In an attempt to study the effect on the electrocardiogram of such rapidly increased intraventricular pressure, records were taken before and after varying degrees of pressure were exerted on the pulmonary artery. Ten anesthetized cats, some decerebrated under anesthesia, had funnel-boot electrodes inserted beneath the skin of both fore legs (on flexors) and left hind leg (on gastrocnemius or vastus), for employment of the three customary leads, the cat lying on the left side. After control records were taken, the thorax was opened under artificial respiration, a Gaskell clamp loosely applied to the pulmonary artery a few centimeters above the valves, and the heart maintained as nearly as possible in its normal position. After another control record, increasing amounts of constriction were exerted by means of the clamp, and records taken as frequently as possible after each quarter turn of the screw. Sometimes records were taken until the artery was clamped tight; at others when dilatation of the right ventricle occurred visibly, the process was reversed, again with records. Sometimes the experiment was concluded by the occurrence of ventricular fibrillation, or by *A-V* block with increasing slowing of the rate; at others it was possible to repeat the sequence after all pressure had been removed.

It was recognized that the numerous manipulations, occasional asphyxia, hemorrhage, and slight and varying changes in position of the heart in the opened thorax in themselves might produce changes in form of the ventriculogram, though the importance of such items was not appreciated to the extent that it is today. These disturbing factors, plus the varying changes due to differences in speed of increasing pressure on the artery, could account for our inconstant results, which were not possible to solve in the few experiments that circumstances permitted. However, while control experiments, such as shifting body position, gave minor changes in form, they never produced the marked changes shown in these records, changes which largely or wholly disappeared on releasing the clamp. (See Buchbinder and Katz's more detailed observations on this point in the preceding article.) It is safe to conclude that the effect of increasing pressure within the right ventricle, as practised here, was regularly to increase the size of the *P* wave in all leads and frequently to produce extreme ventricular deflections like those seen in congenital heart disease. Sometimes signs similar to those of preponderance of the right ventricle (in the old sense) appeared, and disappeared when the clamp was loosed. When the clamp was about  $\frac{3}{4}$  closed, the right ventricle usually became much congested and dilated with a slow beat, and the electrocardiogram sometimes showed a deep broad *S*<sub>1</sub>, a high broad *R*<sub>3</sub> and in Lead II a deep *Q*, medium *R* and no *S*. The possibility of such changes being due to bundle branch block must of course be borne in mind. The reason why these changes only appeared occasionally was not apparent; and it should

be noted that they are not in accord with Buehbinder and Katz's observations. The *T* wave, when not engulfed in the preceding *S*, sometimes became enlarged, sometimes inverted or diphasic, sometimes coming off near the point of *R* or *S* respectively, or at a new level from an overshoot of *R* (or *S*) or finishing at a new iso-electric period. Small extra waves, as if continuations of the *T* disturbance, were sometimes noted (see No. 63) similar to those discussed by Buehbinder and Katz. It is suggested that changes in the ventricular complex, perhaps resembling those of right or left ventricular preponderance, especially if transient, *may* be due to changes in intraventricular pressure and not always to changes in muscle mass or position of the heart.

It was observed with the naked eye that after prolonged dilatation the auricle beat regularly after the ventricle had stopped, then slowed and stopped also. On two occasions distinctly visible contractions of the superior vena cava were observed, a few centimeters above the junction with the auricle. These were thrown in between the auricular beats (1:8, 1:10, etc.) but stopped 2 and 3 min. before the auricle stopped. It was not possible to record them electrocardiographically.

While obviously no conclusions can be drawn from so few experiments with varying results, it is suggested that more extensive studies, better controlled, of increasing pressure in right or left ventricle should throw light on the nature and significance of abnormal ventricular complexes.

## ARTERIOSCLEROSIS OF THE LUMBAR SEGMENTAL ARTERIES PRODUCING ISCHEMIA OF THE SPINAL CORD AND CONSEQUENT CLAUDICATION OF THE THIGHS.

A CLINICAL SYNDROME WITH EXPERIMENTAL CONFIRMATION.\*

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DEJERINE's syndrome<sup>1</sup> in the syphilitic of "intermittent claudication of the spinal cord" characterized by recurring weakness in the lower limbs on exertion, but which was unaccompanied by cramps or by obliteration of arterial pulsations in foot and ankle,

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was recently observed in 4 non-syphilitic patients who showed roentgenographic evidence of marked arteriosclerosis of the lower abdominal aorta. An ischemia of the spinal cord due to arteriosclerotic involvement of the segmental branches from the aorta was postulated to explain this syndrome, and ligation of these arteries confirmed this hypothesis by producing an identical syndrome in the experimental animal.

**Historical.** Discussions of the effects of arteriosclerosis of the vessels of the spinal cord are conspicuously absent in modern textbooks or monographs of neurology, although the literature of the past century contained many reports of symptoms referable to this condition. More recently there has occurred a revival of interest in the subject and a number of articles have appeared on focal lesions of the cord due to arterial disease<sup>2,3,4,5</sup> and on the resemblance of the early lesions of multiple sclerosis to those of experimental vascular occlusion.<sup>6</sup>

*Intermittent Claudication of Local Vascular Origin.* The early descriptions of intermittent claudication were written by neurologists. Charcot<sup>7</sup> in 1858 first described the syndrome in the horse and in man. He found occlusion of the peripheral arteries with ischemia of the muscles and nerves of the legs. In 1862 Raynaud<sup>8</sup> introduced the elements of vasomotor spasm due to dysfunction of the sympathetic nervous system into the problem, and Erb<sup>9</sup> in 1898 was one of those who added the third type of peripheral vascular disease known as thrombo-angiitis obliterans. Intermittent claudication was explained by some observers on the basis of inadequate blood supply to active muscles, by others to disturbances of innervation. In a similar way the origin of the pain of angina pectoris was debated. To add to the confusion, Dejerine (1894) described a rare form of "intermittent claudication of the spinal cord." Only recently has Thomas Lewis<sup>10</sup> demonstrated that intermittent claudication (and probably angina pectoris as well) is to be attributed to pain which is "determined by some chemical or physico-chemical agency within the mass of muscle."

*Paraplegias.* In addition, certain paraplegias have been attributed to ischemia of the extremities or of the spinal cord. Thus, in 1857, Gull<sup>11</sup> wrote of a sudden paraplegia with paralysis of the sphincters, and anesthesia of the lower extremities in which arterial pulsations were absent. There was a rapid but incomplete recovery, and a tremendous development of subcutaneous collateral arterial circulation. "Examination of the case . . . made it probable that the paraplegia had arisen from some sudden deficiency of arterial supply to the lower extremities, as in the experiment by Sir Astley Cooper of ligature of the abdominal aorta in a dog." On the other hand, Gowers<sup>12</sup> suggested disease of the small arteries in the spinal cord as a cause of senile paraplegia characterized by progressive weakness of the legs and no changes in the reflexes. Bramwell<sup>13</sup> stated in 1886 that "paraplegia sometimes results from

the sudden stoppage of the blood supply to the lower end of the cord, an accident which occurs in the course of some abdominal aneurysms in consequence of detachment of the clot or obstruction of the abdominal aorta. In some cases of aortic regurgitation, weakness in the lower extremities—never, so far as I know, amounting to true paralysis—is seen. The motor weakness probably results from anemia of the lumbar region of the cord.” Bristowe<sup>14</sup> invoked both peripheral vascular ischemia and ischemia of the spinal cord to explain 3 cases of paraplegia following sudden obstruction of the abdominal aorta by aneurysm (1881).

*Blood Supply of the Spinal Cord.* The most valuable description of the vascular supply of the spinal cord is given by Moxon.<sup>15</sup> “The blood-supply to the spinal cord is carried out by slender vessels which come from the vertebral arteries within the cranium. There are 3 of these arteries—1 on the front and 2 on the back of the cord; they are very slender, and yet have to run along its whole length.” Since pressure in these spinal arteries falls rapidly, reinforcing arteries (the cervical, intercostal, lumbar and sacral segmental vessels from the aorta) are sent up along each segmental set of nerve roots. “But when you approach the tip of the cord the supply from below becomes exceedingly precarious, and even apt to fail entirely, because upon the long strands of the cauda equina the small arteries are too narrow and too long to reinforce the cord with any certainty. But at the same time the supply from above has to be furnished with greater difficulty than in the upper regions of the cord, because the original anterior spinal artery is very far away, and the reinforcing arteries even in the lumbar region have to run considerably longer courses than they had in the cervical region . . . . Hence we see that the tip of the spinal cord corresponding to the lower limbs and sphincters is much more weakly organized as to its circulation than are the upper parts of the cord.” Moxon supplemented his theory with injected specimens—the lower part of the cord was consistently poorly injected (even though the cannula was at the femoral artery), and “in no case were the reinforcing vessels on the nerves of the cauda equina injected.”

He explained the selective weakness of the posterior members of animals following small doses of prussic acid and drugs which lower blood pressure to the peculiarities of the vascularity of the spinal cord.

*Intermittent Paraplegias.* Moxon<sup>15</sup> presented a highly interesting discussion of the intermittent paraplegia and incontinence of caisson disease. Quoting Captain Eads (chief engineer of the Mississippi bridge at St. Louis) he says “When the depth of 60 feet had been attained, some few of the workmen were affected by a muscular paralysis of the lower limbs. This was rarely accompanied with pains, and generally passed off in the course of a day or two. As the penetration of the pier progressed the paralysis became more



FIG. 1.—Bismuth arterial injection 1 day after division of abdominal aorta, showing good vascularity of thighs and legs. Incontinence and paralyzed lower extremities were present.



FIG. 2.—Bismuth arterial injection 1 day after ligation of 1 right and 1 left lumbar artery at the site indicated by arrow. Excellent vascularity of thighs and legs. Incontinence and paralyzed lower extremities were present.



FIG. 3.—Case 2. Calcification in the lower abdominal aorta.

difficult to subdue, and in some cases the arms were involved, and in a few cases the sphincter muscles of the bowels . . . an average of at least 9 out of 10 of those affected suffered no pain whatever, but soon recovered'." Moxon's conception of these phenomena was that, under increased atmospheric pressure, the tip of the spinal cord became anemic; if the cerebral circulation increased to compensate for the caisson pressure, then "when there is activity of circulation within the skull, the cerebrospinal fluid is sent out to press a little, hardly within the spinal canal, on those smaller arteries of the spinal cord. So that over-much activity of the cerebral circulation would tend to compress these arteries, and interfere with the straight and narrow economy of the unfortunate end of the spinal cord. I think this is why very studious people get so delicate about the caudal ends of their spinal cords." To explain the occurrence of paraplegia when the workmen left the high pressure of the caisson, Moxon hypothesized that "a general deficiency of supply arises in the previously well-filled channels. This difficulty tells most on the more weakly organized system of supply to the spinal cord." Hence paraplegia and incontinence resulted. Our modern conception would explain this type of caisson disease due to ischemia of the spinal cord produced by emboli of nitrogen gas.

A second cause of intermittent ischemia of the spinal cord is to be found in 3 cases cited by Erb.<sup>16</sup> Under the heading of intermittent spinal paralysis, Erb presented the cases of Macario, Romberg, and Hartwig as "undoubtedly one of the rarest and most remarkable forms of manifestations of malarial infection." Erb's citation of Romberg's case deserves full quotation. "A woman, aged 64 years, after being quite well the day before, was suddenly attacked with paralysis of the lower extremities and the sphincters. Sensibility was unchanged, consciousness clear, the temperature cool, pulse 80, small and empty, no pain in the spinal cord. The next day there was an astonishing change in the condition. The patient can walk again, and void urine voluntarily, and only complains of weakness in the legs. The next morning there was paraplegia again, which had set in at the same hour as 2 days before. A third paroxysm was awaited, which also set in at the appointed time, although without paralysis of the sphincters. Quinine effected a rapid cure."

Nor can we resist giving Erb's discussion in full. "These 3 very remarkable cases have the following features in common: that they all present a rapidly developed paraplegia, advancing to complete motor paralysis, with or without anesthesia and paralysis of the sphincters; that this paraplegia disappears again in the course of a few hours, sometimes with the appearance of a critical sweat, to give place to a complete or well-nigh complete intermission; that this process is then repeated, in a more or less regular manner, in the quotidian, tertian, or quartan type; and that the entire affection is either promptly cured by quinine, or at least favorably influenced thereby.



"It is in the highest degree probable that we here have to deal with a malarial infection; the intermittency of the paroxysms, their termination in a sweat, and the efficacy of quinine, all argue strongly in favor of this intermittent paraplegia being nothing else than a masked intermittent. To be sure, this cannot, as yet, be considered as rigidly proven.

"It may probably be even more positively asserted that the seat and starting-point of this disturbance is to be found in the spinal cord. The entire character and grouping of the symptoms, the limitation of the paralysis to purely spinal nerves, the entire immunity of the brain, the great resemblance to other general paralyses of notoriously spinal origin, speak with such positiveness in favor of this belief that no reasonable doubt on the subject can be raised.

"But it is, unquestionably, a matter of the greatest difficulty to determine what actually takes place within the spinal cord in this malarial paraplegia—whether any, and, if so, what anatomical changes take place therein during the attack. Hartwig assumes that it is a question of transitory hyperemias and serous transudations in the substance of the spinal cord; a supposition which appears to me untenable, from the mere fact that the disturbance is always confined to the motor portions of the cord, leaving the sensory portions entirely free. It is probably safer to say that the essential conditions of malarial spinal paraplegia are at present unknown to us, and that we can only hope for light on this subject from the future."

Two years later, Laveran discovered the parasite of malarial fever (1880); today all textbooks of pathology picture the capillaries of the brain and viscera plugged with pigment and parasites. We may now explain these cases of intermittent malarial paraplegia on the basis of ischemia of the spinal cord as the result of such plugged vessels, with remission accompanying the vasodilatation of the sweat.

**Dejerine's Intermittent Claudication of the Spinal Cord.** According to Dejerine<sup>1,17</sup>, this rare condition is due to a progressive occlusion of the lumina of the arteries to the lower cord, attributed to an arteritis, presumably syphilitic. The disease begins with a weakness, often unilateral, on exertion of the legs. The weakness soon becomes bilateral and develops more promptly on walking. A few minutes of rest permits recovery, progressively less complete. When the resting patient is examined, nothing is found; during a period of fatigue, a certain degree of spasticity may be evident. Soon the tendon reflexes are somewhat hyperactive in repose, more so after walking. At this time the sign of Babinski appears on exertion, to disappear with rest. Deep and superficial sensibility is intact. Urinary symptoms appear, with loss of libido or with hyperexcitability and premature ejaculation; the sphincter ani may or may not escape. Finally a permanent spastic paraplegia supervenes.

Dejerine sharply separated this syndrome from Charcot's intermittent claudication. The distinguishing features of the disease of the spinal cord are the integrity of the arterial pulsations of the lower extremities, the absence of pain and of vasomotor disturbances, and above all the presence of neurologic symptoms: altered reflexes, impairment of sphincter control and genital disturbances. He also differentiated from his syndrome those of pseudoparalytic myasthenia gravis (Erb-Goldflam) and of arteriosclerosis of the vessels accompanying the peripheral nerves; in the spinal cord syndrome, atrophy and changes of electrical reactions are absent, and tendon reflexes are not lost.

**Intermittent Claudication of the Thighs Due to Ischemia of the Spinal Cord.** We have recently seen 4 patients with the syndrome described by Dejerine produced by an arteriosclerosis rather than by syphilis of the spinal cord. In all cases, roentgenograms showed advanced calcification of the terminal abdominal aorta, and in each case there was neither history nor clinical evidence of syphilis. In the absence of autopsy material, we were able to verify experimentally the hypothesis that intermittent claudication of the thighs was due to ischemia of the spinal cord the result of occluded arteriosclerotic lumbar segmental arteries or their branches to the spinal cord. The vascular supply to the muscles involved in this claudication was unimpaired.

**Experimental Confirmation of Claudication of the Thighs from Ischemia of the Spinal Cord.** Weakness of the hind limbs after complete occlusion of the aorta was repeatedly recorded in the protocols of adult animals in Professor Halsted's article<sup>18</sup> in 1909, on partial, progressive and complete occlusion of the aorta and other large arteries in the dog by means of the metal band. As an example, in his Dog 2 with partial occlusion followed in a month by complete occlusion of the abdominal aorta, it was noted "1 hr. after operation the dog was able to climb a flight of stairs. The hind legs were in a spastic condition, flexed on the abdomen, at the knees and hips, and were very much weaker than the fore legs." Forty-eight hours after occlusion "hind legs are dragged in walking but are not completely paralyzed. Movements still spastic." On the 6th postoperative day "bladder and rectum function normally. Scratches himself with left hind leg without apparent weakness." The weakness of the hind limbs suggested an investigation of the spinal cord which was entrusted to Dr. P. K. Gilman "who discovered, in several instances, about 3 months after total or almost total aortic occlusion, a deposit of extradural fat about the cord below the site of the aortic band. In 3 cases the production of fat was so great that it filled, seemingly under considerable tension, the vertebral canal."

Professor Halsted's interest in the collateral circulation after occlusion of large arteries led to a report by Reichert<sup>19</sup> in 1924 in which, among other sites of ligation, the abdominal aorta was ligated in ten instances. "In these studies young dogs were used since adult animals not infrequently show evidence of spinal cord

changes." The study of any effect upon the spinal cord was not undertaken at that time; however, it was the impression in the laboratory (on obtaining apparently good arterial injections of the tissue distal to the aortic occlusion in some adult animals) that the weakness and spasticity of the hind limbs could not be due to impaired blood supply to their musculature but was probably caused by ischemia of the spinal cord.

When the first patient (Case 2), with claudication due to weakness of the thighs, tabetic type of gait, and calcification in the lower abdominal aorta, was studied, these earlier observations in the dog came to mind and the problem was taken to the laboratory. The details of the experimental work will be published separately<sup>20</sup> and only a summary of the results will be given here.

The problem resolved itself into determining the effect on the hind limbs (1) of ligation of the abdominal aorta alone, (2) of aortic ligation in conjunction with ligation of one or more lumbar segmental arteries, and (3) of ligation bilaterally or unilaterally of one or more lumbar segmental arteries. The effects of the ligations were carefully observed by exercising the animals and having them climb stairs. When sacrificed, the whole arterial system was injected through the heart with Poth's<sup>21</sup> modification of Hill's<sup>22</sup> bismuth oxychlorid mass, opaque to the passage of Roentgen rays. Stereoscopic roentgenograms were examined to determine circulatory alterations following ligation. The spinal cord and its coverings were excised, roentgenograms taken to show its arterial injection, and section of the cord studied microscopically and by the clearing method of Spalteholz.<sup>23</sup>

*Ligation of the Abdominal Aorta.* In our previous experiments<sup>19</sup> it was shown that some degree of collateral circulation was normally present when the aorta was injected immediately after its ligation and division, the bismuth appearing in the trifurcation and its branches well down into the legs. Injections made 10 to 12 days after ligation showed complete filling of the vessels distal to the ligation.

In the present study the abdominal aorta was ligated in 3 adult dogs. One old dog who was paralyzed and incontinent was sacrificed and injected 24 hr. after division of the aorta. The roentgenograms (Fig. 1) showed good arterial injection in the thighs and legs but not equal to that in Fig. 2 where the aorta was intact. The day after ligation the remaining 2 dogs walked poorly, dragging the hind legs. Only a few steps were climbed before the hind quarters gave way. The following day they were unable to climb, weakness of the hips was quite noticeable, and a scissor-like gait appeared. By the 7th day after ligation they were up and about with definite but slight weakness of the hind limbs and slight swaying of the hips. After 2 weeks the hind limbs seemed spastically extended, with stiffness noticeable in the upper thighs.

*Bilateral Ligations of Lumbar Arteries.* In 5 adult dogs one or

more pairs of lumbar segmental arteries were occluded as they branched from the aorta. A very old dog, after ligation of 1 right and 1 left lumbar artery was totally paralyzed in her hind limbs and was incontinent. When injected 24 hr. after ligation the arterial eggs (Fig. 2) was excellent indicating that filling of the thighs and legs was due to impaired vascularity of the musculature of the hind limbs. The weakness of the hind limbs developed when the abdominal aorta was ligated on the 5th day and could not be detected at the end of a month. In a young adult animal weakness of both hind limbs was evident for 3 days after ligation of a lumbar artery on each side. A week later 2 distal lumbar arteries on each side were ligated but no weakness developed. Roentgenograms of the injected animal showed that considerable collateral circulation had developed after the first ligation, which was adequate in supplying the region involved in the second ligation. In another young adult animal, when 4 lumbar arteries on one side and 1 artery on the other side were ligated, the hind limbs seemed equal but the subsequent weakness of the thighs and legs was marked on the side of the 4 ligated arteries. When 3 lumbar arteries were ligated on each side the weakness gradually improved over a period of 2 weeks, with spasticity appearing 2 days after ligation. Climbing a short flight of stairs could not be accomplished until the 8th day after ligation.

*Comment.* The ligation of one or more paired lumbar arteries produced effects almost identical and as severe as after ligation of the abdominal aorta. In fact, in a very old dog ligation of a single pair of lumbar arteries caused paralysis and incontinence; yet the roentgenograms of the injected animal (made 1 day after ligation) showed no interference with the circulation to the lumbar region or the hind limbs, although the ligated arteries were not as fully filled with bismuth as the adjacent ones. Development of sufficient collateral circulation through the adjacent lumbar arteries in the other cases seemed to explain the improvement in symptoms that occurred within a week after ligation.

These experiments produced symptoms similar to those observed after ligation of the abdominal aorta and the arterial injections proved that it was not the impaired circulation to the musculature in either case but the ischemia of the spinal cord that produced the weakness of the hind limbs.

*Ligation of the Abdominal Aorta and One or More Lumbar Arteries.* Ligation of the abdominal aorta has never produced gangrene, nor does gangrene occur after ligations of 3 pairs of lumbar arteries. In 2 of 3 experiments in which in addition to aortic ligation one or more pairs of lumbar arteries were also occluded, complete paralysis and with massive gangrene developing distally from the midabdominal region. The young adult animal that

survived had marked weakness of the hind limbs and was incontinent for a day. Three days after ligation his hind limbs were stiff and he would take only a few steps. Four days later he walked readily but with stiff hind limbs, and awkwardly went up and down stairs. Ten days after ligation he walked and jumped about readily and showed only a slight weakness of the hind limbs on climbing stairs.

*Unilateral Ligation of Two or More Lumbar Segmental Arteries.* In 4 animals 2 lumbar arteries and in 1 animal 3 lumbar arteries on 1 side only were ligated. All had weakness and some stiffness of the corresponding hind limb lasting from 3 to 8 days.

*Comment.* This ipsilateral weakness and spasticity after unilateral ligation of 2 or 3 lumbar segmental arteries added further proof to the preceding results that ischemia of the spinal cord produced the weakness of the hind limb, since the roentgenograms of the injected animals showed no impairment of the arterial supply of the involved musculature at the time of greatest weakness (2 or 3 days after ligation).

**Summary of Experimental Results.** In adult dogs the signs of weakness of the hind limbs, especially in the hips and thighs, accompanied at times by temporary incontinence, and associated with a delayed spasticity, invariably followed either ligation of the lower abdominal aorta or ligation bilaterally of one or more lumbar segmental arteries. Ligation of one or more lumbar arteries on one side only invariably produced weakness of the ipsilateral hind limb. In these experiments exercise resulted in weakness only, never any apparent pain. Bismuth arterial injections made through the heart filled the entire arterial system as shown in the stereoscopic roentgenograms and revealed that the weakness was not caused by inadequate blood supply to the involved muscles but could only be due to ischemia of the spinal cord. With the development of adequate collateral circulation through adjacent lumbar arteries the signs rapidly improved.

The chief complaint of our 4 patients was weakness on exertion of the upper thighs, especially of the anterior group of muscles. That type of pain characteristic of the ordinary intermittent claudication was conspicuously absent. The neurologic examinations revealed only hyperactive deep reflexes. Blood and spinal fluid examinations were negative for evidence of syphilis and of pernicious anemia. Signs and symptoms of generalized arteriosclerosis were obtained and all exhibited calcification of the terminal abdominal aorta in the roentgenogram.

**Case Reports.** CASE 1.—(E. L. B.) Mr. F. O. S., aged 69, when first examined March 30, 1927, presented a history of 3 years' duration of a gradual increase in the feeling of numbness of the bottoms of both feet (although sensation was normal) and marked weakness of both quadriceps muscles. These symptoms were preceded by cerebral arterial trouble with diplopia and hypertension. After slight exercise considerable weakness of the quadriceps and other thigh muscles developed which left him unable

to control his legs and feet. Urinary symptoms (hesitancy and difficulty in feeling the passage of urine) were present for several years. There was no pain.

Examination revealed generalized arteriosclerosis with pulsations in the pedal arteries much decreased but still palpable. The thighs and legs seemed spastic, and the weakness of the thighs with inability correctly to place the feet presented a gait resembling that of a tabetic. The reflexes were hyperactive. There were no signs and the examinations were negative for pernicious anemia and for syphilis. The prostate was twice normal size. Roentgenograms showed definite calcification of the lower portion of the aorta just above the bifurcation.

*Comment.* In the presence of generalized arteriosclerosis one explanation for the claudication in the thighs would be sclerotic changes in the vessels to these muscles, but the absence of pain, the patent pedal arteries, the feeling of numbness in the feet although the sensation was normal, the difficulty in recognizing the passage of urine, the steppage gait, and the calcification of the abdominal aorta strongly favored an ischemic condition of the spinal cord as the correct explanation.

CASE 2.—(D. A. R. and F. L. R.) Mr. A. B., aged 53, a salesman, entered the neurologic wards of Lane Hospital December 1, 1932, complaining of burning in the legs and feet and inability to control his lower extremities when walking, for 2 years. Weakness and cramps developed in his thighs and legs on walking up an incline or up steps. When climbing stairs it was necessary to use the hand rail, as his hips and knees would give out and he would collapse. After walking 2 or 3 blocks his thigh and calf muscles would tighten and become painful so that he walked stiffly. The pains in the thighs were mainly anterior. Bowel trouble, described as a sense of fullness in the rectum and soiling of the linen, was another complaint. The diagnosis of tabes by the examining officer was made from his gait and could not be confirmed in the ward. Complete examinations ruled out pernicious anemia and syphilis. There were no neurologic signs except hyperactive reflexes. Pulsations of the dorsalis pedis artery were absent on the right and barely perceptible on the left. Roentgenograms taken of his pelvis because of pain and weakness in the hips were negative except for calcification in the terminal abdominal aorta and right iliac artery (Fig. 3).

In an attempt to relieve his claudication a bilateral alcoholic sympathetic block at the level of  $L_1$ ,  $L_2$  and  $L_3$  was made which warmed both feet and toes and relieved the burning sensation. Six weeks later pulsations were readily felt in the left and just perceptible in the right dorsalis pedis artery, but he had no definite improvement in the claudication.

*Comment.* This patient with claudication of the hips and thighs, stiffness of the limbs, and calcification in the abdominal aorta reminded us of the dogs reported by Dr. Halsted with weak hind limbs after occlusion of the abdominal aorta and led to the experimental study of signs obtained from vascular impairment of the spinal cord summarized in the preceding section. His syndrome was a combination of the ordinary type of intermittent claudication with pain in the muscles, with claudication due to weakness but without pain; the former is attributed to ischemia of the muscles,

the latter to ischemia of the spinal cord. In this patient, both types occurred together or alone at various times.

CASE 3.—(F. L. R.) Dr. S., aged 57, noticed early in January, 1932, that walking 10 blocks easily fatigued him and produced dizzy-spells with nausea and vomiting. On January 18 he developed a coronary occlusion with a systolic pressure of 80. Four days later the systolic pressure was 100 to 106. During the 5th week he could not get comfortable in bed, feeling the substernal pain and pain in the back, particularly between the shoulders, or pain in the gluteal region.

Within a  $\frac{1}{2}$  hr. after sitting up on the edge of the bed for the first time in 10 weeks he suddenly coughed up blood tinged sputum and later noted a tingling sensation in the fingers of the right hand and in the toes and sole of the left foot. This sensation continued for 3 weeks and gradually disappeared, to reappear and remain for over  $1\frac{1}{2}$  years. At the same time the skin of the left upper chest was extremely painful to the slightest touch. Frequently pain of a burning character would extend down both arms as far as the wrists.

Frequent blood-pressure readings taken as soon as the patient became comfortable after paroxysmal attacks of weakness almost invariably showed the systolic reading at 100 or less, and when he was feeling fairly well this pressure varied from 110 to 125.

When seen on April 8, 1933, he had been complaining for several months of weakness of both thighs, difficulty in walking on the level with shuffling of his feet and inability to walk up hill or up stairs. Pulsations were readily obtained in the feet and ankles, and the reflexes were hyperactive. The tingling sensation in the right hand and left foot persisted.

The history of weakness in both thighs was similar to the complaint of the previous patient so that there was no surprise when roentgenograms revealed calcification in the abdominal aorta and some of its pelvic branches, and also in the left coronary. On a month's régime to maintain and increase his blood pressure, walking improved and the gait became spastic, suggesting even to him that of a tabetic, although all examinations for syphilis were negative.

*Comment.* A subnormal blood pressure with periods of markedly low systolic readings prevailed throughout his convalescence. The evidence of arteriosclerosis in the abdominal aorta, yet with excellent arterial pulsations obtainable in the extremities, would favor the diagnosis of ischemia of the spinal cord as the cause of the claudication of the thighs and the "tabetic" gait.

CASE 4.—(E. L. B.) Dr. W., dentist, aged 45, was referred by Dr. L. Falk February 13, 1933. In July, 1932, the patient gradually experienced tiredness in the anterior portion of both thighs on walking; especially up hill. There had been no cramps in the calves nor any neurologic symptoms.

The examination showed absent pulse in both dorsalis pedis arteries and in the left posterior tibial vessel. The pulsation in the right posterior tibial artery was barely palpable. His blood pressure was 155 systolic, 100 diastolic. The reflexes were all present, equal, and hyperactive. Physical and serologic examinations were negative for syphilis. Roentgenograms of the lumbar spine, thighs, and legs showed definite calcification of the aorta from the third lumbar vertebra down to the bifurcation, with no evidence of sclerosis in the peripheral vessels.

*Comment.* Claudication limited to the thighs without arteriosclerotic symptoms elsewhere and with calcification of the arterial

tree limited to the lower abdominal aorta is difficult to explain except as an ischemia of the spinal cord.

**Conclusions.** The ordinary intermittent claudication in the arteriosclerotic is characterized by pain which is attributed to physiologic processes developing in the working muscles easily fatigued due to impaired blood supply. It is associated with a lack of arterial pulsation in the feet and ankles, color alterations in the skin of the extremities on change of posture, and roentgenographic evidence of calcification in the arteries of the legs.

Intermittent claudication because of weakness in the thighs and hips was the chief complaint of 4 non-syphilitic arteriosclerotic patients who exhibited a spastic gait resembling that of a tabetic, who had no positive neurologic signs, and whose roentgenograms revealed calcification in the lower abdominal aorta.

The claudication of the thighs in these 4 patients was attributed to ischemia of the spinal cord produced by alterations in spinal branches of the arteriosclerotic lumbar segmental arteries arising from the abdominal aorta.

This hypothesis was strengthened by roentgenographic evidence of calcification in the terminal portion of the abdominal aorta and by experimentally produced claudication in the thighs of adult dogs after occlusion of the lumbar segmental arteries without interference with the blood supply to the thighs or remainder of the lower extremities, as shown roentgenographically by complete arterial injections of the animals.

Unilateral claudication developing after ipsilateral occlusion of one or more lumbar arteries in the dog afforded further proof that ischemia of the spinal cord was the cause of the claudication.

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## THE TREATMENT OF ARTERIOLAR HYPERTENSION WITH CRYSTALLINE OVARIAN HORMONE (THEELIN).

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A CAUSATIVE relation between the endocrine system and arteriolar (essential) hypertension has often been suggested and in some cases proven. In one group of cases, namely, hypertension associated with tumors of the suprarenal gland, the evidence of an etiologic relationship is adequate.<sup>1</sup> The ovaries have often been mentioned as concerned in the development of arteriolar hypertension, but there is very little evidence. In an analysis of 1230 menstrual and sex histories taken with this possible endocrine relation in mind, Alvarez and Zimmerman<sup>2</sup> found that hypertensive women showed a much higher incidence of sexual abnormalities such as uterine fibroids, a masculine distribution of body hair and sexual anesthesia as compared with women having normal blood pressures. These investigators believed their evidence supported the theory that arteriolar hypertension is a "bodily peculiarity inherited equally by girls and boys, but ordinarily repressed in women before the menopause by the ovarian or other related secretions." Such a theory explains why arteriolar hypertension increases in frequency at and beyond the time of the menopause. Also, the absence of the female sex hormones in men may be the reason why arteriolar hypertension begins earlier in men.

Which one, if any, of the sex hormones, is related to the development of arteriolar hypertension is also a surmise. Since it is known that, at the time of the menopause, the ovaries atrophy and their secretions probably cease, it is possible that the ovarian hormones are the ones concerned in the development of the disease. In the past, various investigators have reported that extracts of the ovary lower blood pressure, but it is now recognized that these preparations were inert or contained non-specific vasodilators such as cholin.<sup>3</sup> Recently, Doisy<sup>4</sup> isolated the first female sex hormone in crystalline form, the ovarian follicular hormone called Theelin. Several studies have already been made concerning the effect of this hormone on the

blood pressure. Laquer<sup>5</sup> using a preparation called Menformon, which is probably the same as Theelin, found no effect on the blood pressure of animals. Melchionna,<sup>6</sup> using Theelol intravenously, also found no effect on the blood pressure of anesthetized animals. However, Crainicianu<sup>7</sup> and his coworkers have reported strikingly different results. These investigators, using Menformon and Hogival brands of the hormone, found that a drop in blood pressure followed the intravenous injections of 100 rat units in animals, especially in females. In addition, Crainicianu studied the effect of 100 rat units injected intravenously into 100 human subjects with apparent success except in castrated women. Unfortunately, these apparently important results of Crainicianu are presented in such a way as to make anyone familiar with the variability of both normal and high blood pressures, highly skeptical of the method by which Crainicianu obtained his results. He did not mention that he in any way controlled the study of his subjects' blood pressure before giving the injections of hormone. The cautions needed for any study of blood pressure have frequently been emphasized.<sup>8</sup>

**Present Investigation.** In the present investigation, the effect of the ovarian follicular hormone upon the blood pressure, catamenia, and symptoms of patients with arteriolar hypertension has been studied. The ovarian follicular hormone used is marketed under the names of Theelin and Theelol.\* Both Theelin and Theelol are each a distinct crystalline chemical compound, the Theelin being active only on hypodermic injection, whereas, Theelol is active when administered by mouth. Theelin was supplied in 1 cc. ampules containing 50 rat units. The Theelol was used in two different strengths, a tablet triturate containing 100 rat units, and in capsules each containing 50 rat units.

The small number of patients used for this study seems well compensated for by their variety and by the length of their control observation prior to this study. Of the 10 patients studied, whose ages varied from 36 to 60, 2 were males and 8 were females. Of the 8 females, 3 had not reached the menopause while 5 had long passed the menopause. The renal function was normal in all the patients. Electrocardiograms in 9 of the patients showed that the only abnormality (in 5 patients) was moderate left axis deviation. Teleoroentgenograms taken in all the patients showed moderate cardiac enlargement in 5 patients. In 6 of the 10 patients, the ocular fundi showed moderate to marked narrowing of the arterioles, while in Patients 7 and 9 there were little or no change.

All of the patients had been seen by the author over a period of at least 1 year before this study, and during that time had each made an average of 11 visits at average intervals of 1 month. On each of these visits during the year preceding this study, the blood-pressure measurements were made in the same way as during the present study—as follows: On arriving at the clinic or office, the patient sat resting until his turn for examination. Then after entering the examining room, and lying down on a table, his blood pressure was taken at once by the author. Then he was urged to relax and allowed to rest alone in the examining room. At intervals of 10 min. the blood pressure reading was taken over a period of 20 min. In 9 of the patients the systolic pressure was above 160 mm., and the diastolic above

\* Dr. E. A. Sharp, of the Parke, Davis & Co., supplied generous amounts of the hormone.

95 mm. while in Patient 9 the systolic reading fluctuated between 140 and 160 mm. and the diastolic 80 to 94 mm.

In addition to this average control period of 1 year, during which little or no medication had been given, a special 3 to 4 weeks' control period was instituted before the start of Theelin therapy (Table 1). At start of this

TABLE 1.—AGE, SEX, DOSAGE AND DURATION OF TREATMENT WITH THEELIN AND THEELOL OF PATIENTS WITH ARTERIOLAR HYPERTENSION.

Patient No.	Age.	Sex.	Period of water injections (weeks).	Amp. 1 (50 R. U.) daily of Theelin (weeks).	Amp. 2 (100 R. U.) daily of Theelin (weeks).	Additional daily dosage (weeks).
1	58	M.	4	5	2	100 R. U. Theelin by injection } 200 R. U. Theelol by mouth } (4 weeks)
2	43	F.	3	3	5	
3	57	F.	4	6		
4	60	F.	4	2		
5	47	F.	3		5	50 R. U. Theelin by injection } 300 R. U. Theelol by mouth } (2 weeks)
6	49	M.	4	3	5	
7	36	F.	4	3	4	
8	59	F.	4	4	2	
9	48	F.	4	3	3	
10	43	F.	4	4	3	

special control period, the patients were taught how to give themselves subcutaneous injections. They were then given 7 ampules each containing 1 cc. of distilled water, and were instructed to inject into themselves daily the contents of 1 ampule. The ampules were of the same size and appearance as the ampules of Theelin later used. The patients returned each week for study of their blood pressure and to receive a supply of ampules of distilled water. The patients, of course, were unaware that they were using distilled water. Thus, this control period permitted proper evaluation of the effect of the frequent visits<sup>s</sup> and supposed treatment<sup>s</sup> upon their symptoms and blood pressure.

Then, without the patient's knowledge, the distilled water ampules were changed to ampules of Theelin, and the routine of weekly visits continued. The Theelin and Theelol treatment was continued for from 1 to 3 months in the different patients. Since stopping the treatment the patients have continued under regular monthly observation for at least 7 months. The dosage administered (Table 1) was varied at different times and in the different patients. In most of the patients, following the control period of distilled water, a daily subcutaneous injection of 50 rat units was taken over periods ranging from 3 to 6 weeks. Following this, the dose was raised to 50 rat units injected twice daily, and continued for 2 to 5 weeks more. Finally, 2 patients (Cases 2 and 7) received massive doses as follows: Patient 2, continued on for 4 weeks during her 3d month of Theelin treatment, with a dosage of 100 rat units Theelin daily by injection and 200 units daily of Theelol by mouth. Patient 7, after an 8-weeks rest period without treatment, took 50 rat units Theelin daily by injection plus 300 rat units of Theelol daily by mouth, for a period of 2 weeks. The largest total dosage was taken by Patient 2, who took 6335 rat units in a period of 3 months.

Results. In no way was any influence on the blood pressure noted. Chart I illustrates the manner in which the blood pressure was unaffected by treatment for as long as 3 months and with high dosage. In fact, during the 6 weeks' control period with distilled water, the blood pressure appeared to be lower, and then appeared to rise on starting Theelin treatment. However, this paradox

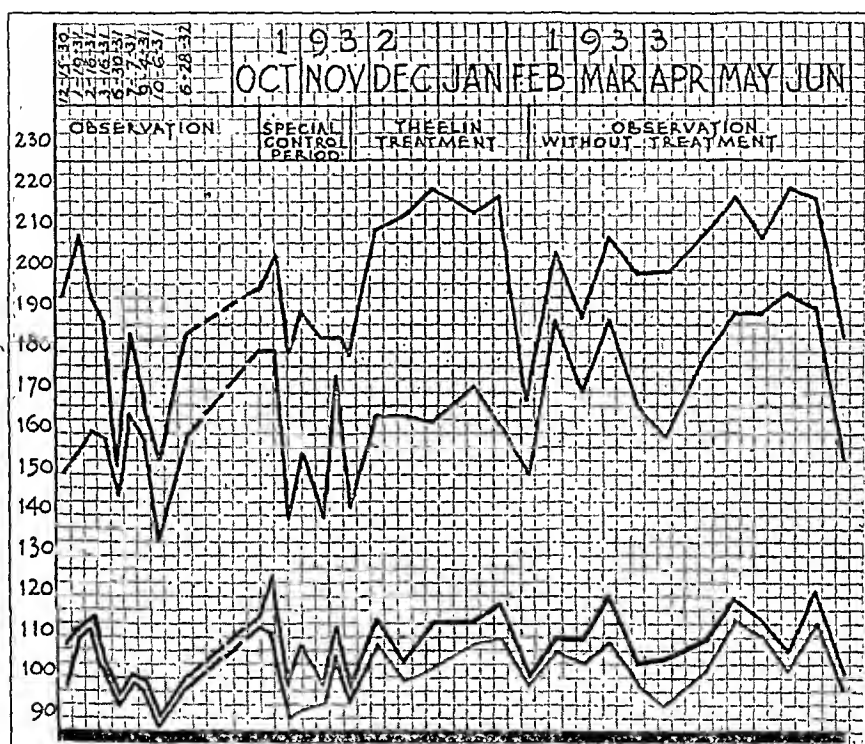


CHART I.—Blood-pressure readings of Patient 2 before, during and after Theelin treatment. The shaded area bounded by the 2 upper curves represents systolic variations, not only from visit to visit, but also after resting at each visit (the latter variations indicated by the vertical distance between the 2 curves). The shaded area bounded by the 2 lower curves represent the same for the diastolic blood pressure.

is due to the fact that during the control period the patient was seen at frequent (weekly) intervals, compared to once in 2 weeks when Theelin was started. The effect of frequent visits *per se* on the blood pressure has been demonstrated before by the author.<sup>8</sup> Most of these patients were symptomless, but as is expected,<sup>8</sup> some of them felt even better while taking the distilled water. In only 1 patient (Case 7) was any effect noted upon the menstrual cycle. In this patient, her second menstrual period after stopping treatment was prolonged from the usual 5 to 6 days to 10 days. This had never occurred before in this patient's catamenial history. However, at this time, she also had a severe attack of common cold. In this same patient, after an 8 weeks' period without treatment the

hormone was again given in large doses for 2 weeks. During the second week of this dosage, she had severe epistaxis twice and a gastro-intestinal upset consisting of epigastric discomfort, nausea, gaseous eructations and pyrosis. Her next catamenia was normal. The catamenia of the other patient receiving large doses was not affected nor were any symptoms produced. All of the female patients were questioned as to their sexual sensations and none admitted any change in sex desire during or after treatment.<sup>9</sup> Patient 4 developed a coronary occlusion during her second week of treatment with Theelin. There seems no reason to believe that the Theelin produced the coronary occlusion.

**Summary.** The effect of the crystalline ovarian follicular hormone (Theelin and Theelol) upon the blood pressure of patients with arteriolar hypertension has been studied. The daily use of this hormone over periods as long as 3 months and in daily doses as high as 350 rat units was without any discernible effect on the blood pressure of these patients.

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#### ERRORS OF SURGICAL DIAGNOSIS.

##### A STUDY OF THE RECORDS OF THE FIRST SURGICAL DIVISION OF THE ROOSEVELT HOSPITAL COVERING A PERIOD OF 3 YEARS.

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As in most institutions of its kind, a regular weekly conference of each surgical division is held at this hospital. The list of operations performed during the week is read, together with a record of instances of lost asepsis, of institutional complications, and, most important of all, of errors of diagnosis. Mistakes of observation or of judgment are noted, commented upon and discussed with a view to the avoidance of similar errors in the future.

From the records of these conferences covering a period of 3 years the diagnostic errors of the First Surgical Division have been tabulated. The histories, physical findings, laboratory data, operative results and pathologic reports of the cases concerned have been reviewed and analyzed. In making this study three questions have been kept primarily in mind: What errors do we most commonly make? Why do we make them? and How may they best be avoided?

**Method.** These errors are determined as follows: Before each operation the anesthetist inquires of the operating surgeon: "What is the pre-operative diagnosis?" The surgeon's reply, his final and considered estimate of the situation confronting him, is entered on the anesthetist's chart and thus becomes a matter of record. At the conclusion of the operation the postoperative diagnosis is also asked for and entered. This latter diagnosis is also subject to confirmation by the subsequent pathologic report. A discrepancy between these recorded diagnoses represents a diagnostic error. If, for example, the diagnosis before operation has been chronic appendicitis and the condition is found to be acute, a diagnostic error is recorded. According to the rules such convenient subterfuges as "exploratory celiotomy" are not encouraged. Each patient is operated upon for some specific disorder which the operator must name. If the condition is not found as predicted, the surgeon must revise his estimate of the situation and seek the sources of his error.

**Results.** *Acute Appendicitis.* In reviewing the errors of these 3 years we find, as might perhaps be predicted, that acute appendicitis heads the list. Aside from the possible complications which may confuse the diagnosis of this condition, two important factors enter into this preponderance of error. The first is that numerically the operations for this condition exceed all others. The second, that it is a diagnosis, which, from the nature of the illness, must be made rapidly and when made, acted upon promptly. During the 3 years under consideration the diagnosis of acute appendicitis has been made 389 times on our division, incorrectly in 28 instances; constituting an error of 7%. That this error is no larger speaks well indeed for the accuracy of succeeding house-surgeons, upon whose shoulders the determination of this diagnosis most directly falls.

Five times, in the 28 errors, acute salpingitis or salpingo-oöphoritis was mistaken for acute appendicitis. The signs and even the history of these two conditions may be very similar, even to the vomiting and early epigastric pain. The lack of Ethiopian antecedents and unconventional social habits may arouse our suspicion, or there may be a vaginal discharge, a tender fornix or an unusually low abdominal tenderness to put us on our guard. Sometimes these signs fail, however, and the differential becomes difficult. One sees, of course, instances of peri-appendicitis of pelvic origin, and on one occasion at least I recall a much inflamed ovary and tube which presented immediately upon opening the peritoneum in a McBurney incision,

while the appendix lay, quite harmless, low down in the pelvis. The hazards of acute appendicitis being what they are, it seems that we must continue to give the patient the benefit of the doubt in the questionable case even though this policy is productive of a certain margin of error.

The next most common source of error in diagnosing acute appendicitis lies in the appendix itself: 5 of our 28 errors occurred in cases where the appendix was not acutely inflamed, as predicted, but was pronounced "chronic appendicitis" by the pathologist. Such an error seems a little difficult to understand, and one would not be likely to expect that it would be made as often as confusing acute salpingitis with appendicitis. Yet it occurred just as frequently in this group. Perhaps a little light on this occurrence may be shed by referring to a case recently operated upon. In this patient, a child, the classical picture of an acute attack of appendicitis was present. Elevation of temperature, high white cell count and relative polynucleosis were all present as were local and rebound tenderness and rigidity. Yet the pain was not persistent, but came in cramp-like spasms so suggestive of ureteral colic as to lead to a Roentgen ray examination before operation was undertaken. Yet this type of pain gave the clue to what was subsequently found at operation—a long appendix, containing fecoliths, markedly kinked near the base by a short mesentery. There was engorgement, but no acute inflammation, the case being one of true appendiceal colic and potentially, although not actually, acute appendicitis. The pathologist reported chronic appendicitis.

Our records bearing on this error indicate that 3 of the 5 cases recorded as wrongly diagnosed fell in this group of obstructed appendices, typified by the example cited. Such appendices may or may not go on to acute inflammation at the time or subsequently. They are probably safer out of the abdomen. The error of diagnosing them as acutely inflamed may perhaps be diminished by considering the duration of the attack and the character of the pain. There are many cases of true acute inflammation encountered in which a history of colicky pain early in the attack may be elicited.

The other 2 of the 5 errors in this group were in patients who had suffered previous attacks of appendicitis and in whom the severity of the current one was overestimated.

In the group of 28 errors there were 4 instances in which normal appendices were removed where the diagnosis was subsequently determined as enteritis. Three of these were in children. In looking back over these records one sees in each case symptoms, signs and laboratory findings sufficiently indicative of appendicitis to lead one fully to expect to find it. Perhaps we have become so imbued with the idea of the vital seriousness of appendicitis in childhood, that we are a little prone to forget that an acute gastro-enteritis may at times simulate it very closely, even to the blood count.

This attitude may be further strengthened by the experience of every surgeon, who can recall instances in which the classical evidence of acute appendicitis were wanting in greater or less measure—yet where fulminating appendiceal pathology was discovered at operation.

Usually, in gastro-enteritis, the rather early onset of diarrhea is a helpful point in our differentiation—yet even this fails us where the apparently inescapable and often lethal laxative has been administered. Further confusion arises from the fact that we occasionally see an appendicitis, especially in children, following and presumably having its inception in an enteritis.

Closely allied to the enteritis group in our record of errors are those cases, simulating appendicitis, in which, at operation, a typhlitis is found. This error occurred 3 times in the 3 years under consideration. Each time the cecum was found much reddened, with thickened serosa and injected vessels, while the appendix, obviously not the source of the difficulty, was but little if at all involved. One might perhaps have been warned in these cases by the fact that the blood counts were not elevated to the degree one might have expected from the severity of the symptoms and signs. Yet, unfortunately, such is often the case in true appendicitis. Although all of these patients survived (except 1 in whom the appearance of the cecum strongly suggested tuberculosis, and who was pregnant as well) they were not benefited by the removal of an appendix in a disease which would no doubt have subsided spontaneously.

The same may be said of the two children who were found at operation to be suffering from serous peritonitis instead of the appendicitis which they were supposed to have. In these cases the abdomens were quite full of straw-colored clear fluid and, except for a rather striking enlargement of mesenteric lymph nodes, no lesions were found. Cultures and sections of removed glands and of appendices revealed no clue as to the nature or cause of the difficulty, and we are still in the dark. Whether this is primarily an intestinal infection, a mild form of pneumococcus peritonitis, or a manifestation of the more or less apochryphal intestinal influenza we are unable to say.

Pneumonia was mistaken for appendicitis but once. Here the Roentgen ray has undoubtedly helped us in keeping the errors low by its ability, in suspected cases, to demonstrate pulmonary lesions before their physical signs become apparent.

Pelvic disease, other than salpingitis, has tripped us more than once, and until our gynecologic diagnostic ability has advanced beyond our present limitations and approaches that of the specialists in that field, will no doubt do so again. The record runs: hematometra, 1; papillary cyst—adenoma of ovary with twisted pedicle—1; ruptured chocolate cyst of the ovary, 1. Certainly, we are con-



vinced by our experience that no female patient should be operated upon for acute appendicitis who has not been accorded a vaginal, or, in the rare instances where this is injudicious, a rectal pelvic examination.

Acute cholecystitis, in low lying gall bladders, was twice mistaken for appendicitis. Ordinarily, the differentiation does not involve great difficulty, it would appear; but there are high placed appendices and gall bladders which descend almost to the pelvic brim to confuse us at times. Their variations between these extremes of position leaves room occasionally for doubt, but the hot gall bladder usually, wherever placed, presents a firm and exquisitely tender area close to the examining fingers, while the high appendix, retrocolic as a rule, withdraws its tenderness behind a shield of resistant muscles rather out toward the flank.

Two other errors in this group are mentioned merely as curiosities. In 1 case, a carcinoma of the transverse colon with acute obstruction and, in the other, an abscess in a right ectopic kidney were mistaken for acute appendicitis.

*Chronic Appendicitis.* The diagnosis of chronic inflammation of the appendix is one which is reached after considerably more deliberation than that of acute appendicitis. Not altogether undeservedly has this diagnosis diminished in popularity of recent years. The chronic appendix has no doubt covered a multitude of surgical sins in its time. Yet, recognizing this fact, there is still a pathologically and clinically demonstrable group of cases in which a diseased condition of the appendix is responsible for a definite set of symptoms. These are the cases suffering from repeated attacks of acute appendicitis, from more or less continued right lower quadrant pain, from vague digestive disturbances (of the appendix reflex type of which Brewer used to speak), from chronic constipation with pain which does not subside when the constipation is overcome. All of these show, in common, tenderness in the region of McBurney's celebrated point.

During these 3 years chronic appendicitis was diagnosed 213 times. The diagnosis was wrong 5 times—an error of 2.3%.

Three of these errors fall in the field of pelvic diagnosis. In 1 case a retention cyst of the right ovary was found. In 2, chronic salpingo-oöphoritis of the right adnexa was the lesion.

In a measure, the remarks made concerning the confusion of the diagnosis of acute appendicitis with pelvic trouble apply here. The patients in whom these errors were made were given pelvic examinations and reported normal. The observation was at fault. The interesting work, which is recently being done, of visualizing the pelvic organs for Roentgen ray by means of a lipiodol injection, may point the way to a greater degree of accuracy in our pelvic diagnosis in the future.

In 1 case, chronic cholecystitis was discovered at operation, in addition to the expected chronic appendicitis.

It would seem that these findings rather emphasize the importance of carefully investigating, as a matter of diagnostic routine in doubtful cases, the biliary system as well as the stomach and kidneys and ureters and pelvic organs before submitting the patient to an operation for chronic appendicitis. Such a procedure is now the practice on our division.

Two further errors must be recorded under this diagnostic group. In 1 case an appendiceal abscess was discovered, retrocecal and well localized, in a patient who entered on the third day of the last of a series of similar attacks with a temperature of  $99^{\circ}$ , but no mass was felt. The other, showing no lesion at operation, had the appendix removed prophylactically, and the pathologist failed to come to our rescue. I believe we are making the diagnosis of chronic appendicitis less frequently as our diagnostic methods improve.

*Hernia.* Next, in point of numbers, to our errors in the diagnosis of appendicitis, acute and chronic, come the mistakes in the diagnosis of hernia. Superficially, at least, it would seem that even a medical student should be able to diagnose hernia with reasonable accuracy, yet this apparently simple condition has with us a diagnostic error of 5%. In 292 cases in 3 years we were wrong 15 times. Yet, there is some consolation in the fact, perhaps, that the errors have shown a yearly decrease.

Two cases operated upon for inguinal hernia had enlarged rings but no hernial sac. One inguinal hernia with hydrocele proved to have the hydrocele but no hernia. Three supposed inguinal hernias, 2 apparently incarcerated, proved to be hydroceles of the cord. Two others proved to be femoral hernias instead of inguinal. One strangulated hernia diagnosed as femoral proved to be inguinal instead. Femoral hernia was also mistakenly diagnosed in 1 case each of femoral adenitis, inguinal adenitis, femoral varicosity, and psoas abscess. One supposedly strangulated umbilical hernia proved not to be strangulated, while one incarcerated inguinal hernia was mistaken for a varicocele.

This, one might say with reason, is hardly a record to be proud of. The mistakes involving adenitis, varicocele, hydrocele and a psoas abscess stand out like a sore thumb. An error of observation was undoubtedly responsible in each case. These mistakes emphasize the importance of considering seriously and eliminating the various pathologic conditions which may simulate hernia, and particularly the necessity of scrutinizing with greatest care those ostensible hernias which do not reduce. As to the elimination of negative findings at operation, we are now in the habit of making the patient demonstrate his hernia before we undertake repair. If he cannot cough it down or walk it down in the ward, he is likely to be requested to report again some day when the hernia is in view. This Missouriian attitude will in the long run, I believe, save some unnecessary operations. We do not feel that an enlarged external inguinal

ring, or pain in the groin, is a satisfactory criterion of the necessity of repair.

*Cholecystitis.* Next in the order of frequency occur the errors in diagnosis of conditions of the biliary tract. Operation was done for acute cholecystitis but 9 times in the 3 years. In 1 the diagnosis was wrong. In this instance a high, acutely inflamed appendix closely simulated the clinical picture of a fulminating, possibly gangrenous cholecystitis.

For chronic cholecystitis 191 operations were done in the 3 years with 13 errors—an error of 6.05%.

In 2 of these cases no lesions were found to explain the symptoms and clinical findings. In one a gastro-enteroptosis of rather marked degree was discovered. One case had an acute suppurative cholecystitis, which, running an unusually quiet course, was thought to be a chronic inflammation. Two had duodenal ulcer, while the symptoms for which the operation was done were found to be due in the remaining cases to one each of the following conditions: chronic pancreatitis, chronic appendicitis, carcinoma of gall bladder, pelvic peritonitis, tuberculous retroperitoneal lymph nodes impinging upon the common duct. In 2 additional cases firm bands of adhesions across the duodenum were found, without demonstrable gall bladder lesion.

In the diagnosis of gall bladder disease it is perhaps more apparent than in any other abdominal field that one cannot depend wholly upon any single diagnostic method. While the history is often typical and characteristic, it alone may be misleading. Much as the Roentgen ray has done to help in the establishment of a correct diagnosis, especially since the introduction of the intravenous administration of tetraiodophenolphthalein, it is still only possible, often, to report that the suspected gall bladder does not fill and visualize properly. Such was the case in a number of the instances cited above, where an extrabiliary lesion rather than a cholecystitis was responsible for the failure to visualize. It is possible to approach accuracy in this diagnosis only where all findings and factors, clinical, anamnetic and radiologic, can be coördinated, and interpreted in their proper interrelationship to form a complete picture.

Here again, as in chronic appendicitis, an isolated study of the supposedly diseased organ will lead to diagnostic errors. The importance of including a full gastro-intestinal Roentgen ray study in the investigation of cases of suspected gall bladder disease is emphasized by the mistakes recorded. It will be recalled that 4 of the 13 errors represented the discovery of gastric or duodenal lesion instead of disease of the gall bladder. To be sure, this method was employed in the cases cited, as it is routinely on our service, in spite of which the errors occurred. The point is that there would certainly have been many more such errors (since the conditions can simulate each other so closely) were this examination not done.

Diagnosis of calculus in the common duct was made 13 times—erroneously in 3 instances. The error here was high, 23%.

One of these cases proved at operation to be acute yellow atrophy. Her history had strongly suggested common duct obstruction, with "indigestion" of 2 months' duration and right upper quadrant pain for 2 weeks, with vomiting and jaundice. On operation the liver showed characteristic changes. The other two had had previous cholecystectomies for cholecystitis and cholelithiasis and complained of recurring attacks of right upper abdominal pain associated with jaundice. Both were found to have dense adhesions partly or completely obstructing the common duct, and were relieved by operation. No stone was found.

In view of the difficulty of differentiating this latter condition from common duct stone, it might have been wiser to have limited our diagnosis to obstruction of the common duct. Neither of these cases showed the tell-tale Charcot fever which we are so likely to associate with the sudden occlusion of the duct by a ball-valve stone. The Roentgen ray, as yet, cannot help us in making this differentiation.

*Duodenal Ulcer.* Duodenal ulcer was the pre-operative diagnosis 64 times in this 3-year period. In 8 the diagnosis was not verified at operation, representing an error of 12.5%. In 1 case, the stomach and duodenum being found normal, the patient's complaint was ascribed to neurasthenia. In the remaining 7, chronic appendicitis was the postoperative diagnosis.

The reaction to such a finding, as explanatory of a duodenal ulcer history, will depend on the individual to whom it is presented. The comment "Thank God for the appendix" may not be altogether unwarranted. It is only fair to state, however, that in each of the present instances there was found some gross evidence of pathology in the surgeon's friend in the right lower quadrant, and in addition, the laboratory staff reported chronic appendicitis. Moreover, in all the patients but the unfortunate neurasthenic, definite temporary improvement, at least, was observed following appendicectomy.

Unquestionably, we are operating year by year on fewer duodenal ulcers. The characteristic history and apparently positive Roentgen ray findings (such as were obtained in the cases here reported) are tempting us less and less to explore the abdomen. Rather are these patients being submitted to medical care and, unless obstructive lesions exist or develop, are being cured over and over again. Also, there is no doubt that the interpretation of the careful Roentgen ray investigation, to which all duodenal suspects are subjected, is gaining in accuracy and precision. The diminishing diagnostic error in this group, I believe, depends upon these two factors.

An entirely different situation exists in respect to duodenal ulcers which perforate. Here the emergency is acute, and early surgical intervention imperative. During this same 3-year period

the diagnosis of perforated duodenal ulcer was made 19 times, 6 times (31.5%) falsely. In nearly a third of the cases, therefore, in the presence of an acute abdominal emergency, perforated duodenal ulcer was fallaciously determined upon as the cause of the trouble. This is a fair indication of the attitude of the surgeon toward this grave emergency, and of its prominence in his mind as something demanding operation. He would rather be wrong many times in his diagnosis than to risk withholding needed aid in one such case.

Of the 6 errors recorded, 3 cases proved to be acute cholecystitis with cholelithiasis, 1 was a volvulus of the intestine with resulting gangrene, 1 was a perforation of a carcinoma of the sigmoid, and 1 an angina or coronary occlusion. This last mentioned patient gave a surprisingly accurate clinical picture of ulcer perforation, presenting, following his acute onset of abdominal pain, a striking rigidity of the abdomen coupled with exquisite tenderness. Our entire staff saw him, and all agreed in the necessity for exploration. The result was a fatality. The other 5 cases really merited surgical intervention although the diagnosis was wrong.

We have found the Roentgen ray a very valuable help in the necessarily hurried diagnosis of duodenal perforations. The sub-diaphragmatic gas bubble which the examination frequently reveals is almost pathognomonic. Still, where this is not found, where liver dullness is not obliterated, we must still explore if the history and physical findings are typical. It is comforting to realize that the acute abdominal emergencies which may simulate the perforated ulcer—volvulus or other acute obstruction, perforation in some other portion of the intestine, fulminating cholecystitis with or without perforation, acute pancreatitis—all demand surgical aid. Were we able to elicit a careful history from these patients, a thing rarely possible in their distress, we might, perhaps, be able to eliminate some of the errors referable to acute cholecystitis. A history of previous attacks, suggesting cholecystitis, might put us on our guard as to diagnosis, but should not deter us from operating.

*Miscellaneous.* Of miscellaneous errors of diagnosis, not falling in any of these major groups, there were 29 in 3 years. These will not be discussed at length, and only the more interesting mentioned as indicative of the occasional vagaries of the surgical mind, or to point out some pitfall which may in the future be avoided.

One perinephritic abscess proved to be appendiceal abscess—a high retrocecal appendix accounted for the error. One appendiceal abscess proved to be an abscess of the kidney—a ptosed kidney felt as a tender mass in the flare of the ilium caused this one. Two hemorrhoids proved to be carcinomas of the rectum—we are sigmoidoscoping all our hemorrhoid cases now. One acute intestinal obstruction of unknown origin was caused by an inflamed Meckel's diverticulum. Two carcinomas of the stomach proved to be benign

gastric ulcers: often a difficult differential diagnosis, even at operation.

One megacolon proved to be carcinoma of the rectosigmoid. The dilatation of the gut was secondary to a low obstruction which, as may happen, was not visualized because it lay behind sigmoid coils. One carcinoma of the transverse colon proved to be chronic cholecystitis with cholelithiasis. The colon was kinked and distorted by adhesions, simulating neoplasm.

**Summary.** Total cases operated upon, 2340; total diagnostic errors, 110; percentage of errors, 4.6.

This catalogue of errors of diagnosis is presented merely as a record of clinical experience. What has been learned by this experience will, we believe, serve as a guide for the benefit of future patients. There is, it is felt, a real value in occasional analysis of diagnostic error both for the institution and for the individual surgeon.

## BACILLARY DYSENTERY IN CALIFORNIA.

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BACILLARY dysentery is an example of a so-called tropical disease which has a cosmopolitan distribution. The infection may lie dormant in the intestine without symptoms until the clinical disease is aroused by some intercurrent agent. When the incubation period exceeds 1 to 7 days, this is usually the case. The onset thus may be precipitated by some unrelated infection, by indigestion, chilling or fatigue. The onset is usually sudden, with variable fever, and with much increased pain and toxemia in warm climates and with the presence of Shiga strains of bacilli. The watery diarrhea soon becomes dysenteric and is accompanied by abdominal pain, prostration, vomiting and characteristic stools. The severity is influenced largely by the type of bacilli. The Flexner strains are milder and more common in California, and the Shiga type more severe and less frequent.

**Pathology.** A toxin is produced which causes a diffused catarrhal inflammation of the colon, in more severe forms going on to ulceration and necrosis of the mucosa and the production of a typical exudate. The inflammatory process is largely limited to the colon but may extend above the ileocecal valve. The bacilli rarely reach the mesenteric glands and do not otherwise leave the intestinal tract. They are not found, therefore, in the urine. In early stages and in mild cases, there is much stringy mucus and so-called snail-track

ulcers of the mucosa. The process is most intense in the rectum and distal colon, tending to spread upward.

In severe cases the inflammation intensifies to a necrosis, which may go as deep as the muscularis and gives rise to a purple-green diphtheritic membrane. In lighter cases, where discrete ulcers are present, the intervening mucosa is also inflamed, and ulcers tend to be transverse to the intestinal axis, have dirty sloughs in their bases and often there are submucosal connections between them. These ulcers are prone to outlast the acute infection, probably, as in the case of amebic ulcers, because of secondary bacterial invasion. The intestinal wall is not thickened as in the case of amebic colitis. Bacillary dysentery may lead to a chronic state in two forms. The first is accompanied by a persistence of dysentery bacilli, often difficult to culture, and by a frequent positive agglutination reaction in the blood. The second is a form of chronic ulcerative colitis most difficult to cure and an entity in itself. Further toxic effects are seen in the anterior horn cells, and in the production of fever, prostration and complications.

Complications include primarily arthritis, which is more common in rheumatic patients. Neuritis is not uncommon, especially in Asiatics, and may be a result of associated vitamin B deficiency. Conjunctivitis, iritis, otitis and myocarditis are seen. In young children and old people, bacillary dysentery is often a serious and dangerous infection. Much of so-called summer diarrhea is due to dysentery bacilli. Even in adults, typical dysentery is not always present, and the clinical picture may consist of a diarrhea of varying severity with more or less fever.

**Diagnosis.** "In no disease is the laboratory diagnosis of more value than in this. In fact, many cases can only be diagnosed by laboratory means, and it is always a necessary method of establishing the diagnosis, even under epidemic conditions. It is well to remember that the stools of bacillary dysentery are really an inflammatory exudate. Thus they show the characteristic sticky gelatinous mucus, with red cells often in rouleaux, numerous pus cells and desquamated epithelial cells, few bacteria, little odor and numerous macrophage cells which are large endothelial cells resembling amebæ but with no motility. The toxic course with a sudden onset, and the extreme frequency and susceptibility in children are to be noted."<sup>1</sup> Fecal elements are largely or entirely absent from the stool.

The first procedure in diagnosis is immediate, fresh examination of an unstained smear from the stool. This shows the characteristics noted above and, in the presence of characteristic clinical picture, is diagnostic. However, in all cases, this direct examination should be supplemented at once by bacterial culture on eosin and methylene

<sup>1</sup> Reed, A. C.: *Tropical Medicine in the United States*, Philadelphia, J. B. Lippincott Company, p. 115, 1930.

blue media for the dysentery bacillus group. Positive cultures are identified by agglutination and sugar fermentation tests. These procedures are to be left to the bacteriologist. It is the part of the clinician to see that certain definite requirements are met in making the culture. The tubes preferably should be inoculated from a freshly passed specimen and, at the latest, within 6, and preferably 2, hours after its passage. The media should be kept warm until placed in the incubator.

In fresh smears, it is to be noted that bacillary dysentery easily activates an infestation of *Endamoeba coli* and is often followed by the appearance of intestinal flagellates. These should not divert attention from the main issue, which is the presence of dysentery bacilli. *E. histolytica* is less common in association with dysentery bacilli, and if very active amebæ, containing red blood cells, are numerous on the first day, there is less chance of the condition being a bacillary dysentery. Stool smears and cultures must be made at the earliest possible time. It is important to determine the strain of bacilli present, in order that the prognosis can be estimated and in order that treatment may be more highly specific.

After direct stool examination and culture, blood serum agglutination should be done in a competent laboratory against the several Flexner, and the Shiga and Sonne strains of bacilli. After the first 6 days, and in chronic and convalescent cases, agglutination is of paramount value.

Sigmoidoscopic examination is not desirable as a routine, is apt to be painful and may even aggravate symptoms. In chronic cases, the sigmoidoscope is invaluable.

**Means of Spread.** Transfer of dysentery bacilli is from man to man by mechanical or passive conveyance only. There is no specific or necessary vector and no intermediate or reservoir host except man. "The disease spreads from infection directly from patients, rarely from healthy carriers, and commonly from relapsing cases of chronic dysentery where bacilli are shed at irregular intervals. The bacilli may be on contaminated door knobs, latrine seats, fomites, etc., and thence pass to hands, to mouth, or to food or water and thus to mouth. Attendants on a patient are very apt to be infected because of the frequent, sometimes almost continuous stools, the sticky gelatinous nature of the passages, and the ease with which hands and fomites become infected. The danger from latrines used by mild or early cases is equally great. The bacilli are abundantly carried by the house-fly, almost certainly in desiccated form by dust, and contaminated food and fingers play the same rôle as in amebiasis and the typhoids. No age is exempt, but small children are particularly prone to infection. The bacilli are easily killed outside the body, especially by sunlight, so that in water exposed to sunlight they rapidly die, while in cool, shaded water they may survive several weeks. They are easily destroyed



by dilute antiseptics.<sup>1</sup> They die in low acid reactions. Thus their production of lactic acid in mucous flakes leads to their rapid disappearance in stool specimens.

**Treatment.** 1. Initial treatment should consist of bed rest and one dose of castor oil. Diet should be liquid or very soft, containing gruels, jellies, gelatins, beef tea, rice or barley water, arrowroot or sago puddings, and avoiding milk. L. L. Stanley advises feeding 2 ounces per day of dried whey powder in solution. Feedings should be at 2-hour intervals, and the food warm.

2. Regular inspection, at least daily, should be made of the stools, which are an important guide for treatment and for prognosis.

3. In more severe cases, and those not clearing at once with the treatment noted, and where fever is much in evidence, specific polyvalent antiserum should be given, in large and repeated doses, intravenously; 200 cc. of the appropriate serum may be repeated according to indications of fever, number of stools, abdominal pain and pulse. This should be associated with intravenous glucose. The action is antitoxic and, therefore, the effect is less curative as necrosis increases in the colon. Due precautions must be observed for serum sensitivity. Intramuscular injection is less desirable. Small children may be treated intraperitoneally or by rectum.

4. The well-tried sodium sulphate treatment is still to be recommended, in conjunction with the other methods indicated. Sodium sulphate is given in 4-gm. doses in water each 2 hours for 2 days, allowing 6 hours at night for sleep, if possible. After this, the same dose is given each 4 hours until the stools become feculent. In children, castor oil may be given in the same dosage and manner.

5. Pain is best relieved by external heat, absolute bed rest and combinations of belladonna, codein and chloral hydrate. Bismuth subcarbonate in teaspoon doses, 4 times daily, is often of great assistance. Opium is to be avoided.

6. Bacteriophage is worth using, especially in Shiga strain infections. It should be autogenous, if possible. Its actual value is still under debate.

7. Personal hygiene of nurses and attendants is extremely important. The frequent, sticky and mucoid stools easily contaminate linen and hands. It is dangerous to put the fingers in the mouth and frequent washing is necessary. Excreta and linen must be disinfected with crude cresol or phenol, or by boiling. The patient must be isolated and quarantine ought to be maintained until 3 negative stool cultures are obtained over a period of 2 weeks.

**Chronic Bacillary Dysentery.** Chronic bacillary dysentery merges gradually into chronic ulcerative colitis. Many cases diagnosed "chronic ulcerative colitis" are really chronic bacillary dysentery. The diagnosis and treatment are difficult. This status in endemic areas is often a precursor of sprue.

**Incidence and Epidemiology in California.** Since 1916, official

<sup>1</sup> Reed, A. C.: Tropical Medicine in the United States, Philadelphia, J. B. Lippincott Company, p. 113, 1930.

records show the presence of bacillary dysentery in California in sufficient quantity to constitute a definite and constant endemic distribution. Most of the cases have been reported in groups, the larger of these being institutional epidemics. Two observations are of practical aid in this connection: (1) Isolated or first cases need much better and earlier recognition in order to prevent spread into local groups or epidemics. (2) The problem of control of endemic sources needs intensive study. One wonders what the actual morbidity may be in proportion to each 100 cases reported.

The character of the California incidence reported makes of primary importance the immediate isolation of early suspicious cases and makes extremely urgent the rigid control of food handlers, especially in institutions and public restaurants. Undoubtedly, infected food handlers' direct contact with patients represents the chief and possibly only means of spread. Two points of attack need careful attention. In the first case, physicians need education in the safe and proper technique of caring for diarrheal cases in the home and also in the hygiene of food handling in the home. This information should be passed on to mothers and housewives. It should include especially detailed instruction in the importance of contaminated hands in relation to food and the importance of keeping fingers and mouth always apart. In the second case, the sanitary care of patients with diarrhea needs detailed instruction. Better control and examination of food handlers in institutions and restaurants is a crying need and demands attention. Rural districts need inspection and control of water supply, sewage disposal and abolition of open privies.

The chart of incidence of bacillary dysentery in California, appearing below, was prepared by Miss Ida M. Stevens, Supervising Morbidity Statistician of the California State Department of Public Health. Miss Stevens states (personal letter) that "In 1917, the 12 cases of Hiss-Russell-Y type occurred in an Oakland Hospital and the records for the county as a whole are not available. The same is true of Orange County in 1918—a group of 5 cases, Shiga type, were investigated by our epidemiologist, but our morbidity records from 1918 do not include the distribution by counties. This is likewise true of Napa County, in 1916, in which there were 400 cases of H. R. Y type. I might explain that reporting has improved in the last few years. Also there are more laboratory facilities available in the southern part of the state—this might

TABLE 1.—TOTAL CASES OF BACILLARY DYSENTERY REPORTED TO STATE BOARD OF HEALTH FROM CALIFORNIA.

1917	.	.	.	.	.	.	.	12	1925	.	.	.	.	.	.	62
1918	.	.	.	.	.	.	.	5	1926	.	.	.	.	.	.	277
1919	.	.	.	.	.	.	.	0	1927	.	.	.	.	.	.	148
1920	.	.	.	.	.	.	.	119	1928	.	.	.	.	.	.	57
1921	.	.	.	.	.	.	.	19	1929	.	.	.	.	.	.	1168
1922	.	.	.	.	.	.	.	9	1930	.	.	.	.	.	.	113
1923	.	.	.	.	.	.	.	66	1931	.	.	.	.	.	.	150
1924	.	.	.	.	.	.	.	45	1932	.	.	.	.	.	.	302

TABLE 2.—CALIFORNIA STATE DEPARTMENT OF PUBLIC HEALTH. CASES OF BACILLARY DYSENTERY.

County.	Year.	Total cases bac. dysentery Reported.	Types.		
			Shiga.	Flexner.	H. R. Y.
Alameda . . . .	1917		..	..	12
	1920	37	..	..	35
	1921	9	..	4	
	1922	5	..	..	5
	1925	2	..	1	
	1926	4	1	1	1
	1930	4	..	1	1
Butte . . . .	1932	4	..	1	
	1927	1	..	1	
Colusa . . . .	1930	4	..	4	
	1931	1	..	..	1
Contra Costa . . . .	1930	6	..	6	
El Dorado . . . .	1929	1	..	..	1
Fresno . . . .	1931	4	..	1	
Imperial . . . .	1928	1	..	1	
	1932	3	..	1	
	1921	1	..	1	
Kings . . . .	1923	2	..	1	
	1927	7	..	..	7
Lake . . . .	1932	16	..	16	
Los Angeles . . . .	1920	47	6		
	1923	47	..	1	
	1924	41	..	4	
	1925	58	..	2	
	1928	43	14	10	1
	1929	68	..	26	20
	1930	90	4	12	
	1931	141	3	18	
	1932	200	4	40	
	1930	1	..	1	
Madera . . . .	1932	2	..	1	
	1926	27	..	26	
Marin . . . .	1927	138	..	138	
	1929	947	..	946	
	1930	1	..	1	
Mendocino . . . .	1923	1	..	1	
Merced . . . .	1931	1	..	1	
Monterey . . . .	1927	1	..	..	1
Napa . . . .	1916	..	..	..	400
	1929	134	..	134	
	1932	17	..	..	17
Orange . . . .	1918	..	5	..	
	1923	5	1	..	
Placer . . . .	1929	5	..	..	5
Riverside . . . .	1928	2	..	2	
	1932	3	1	..	
Sacramento . . . .	1929	1	1	..	
	1930	6	2	4	
	1932	4	..	1	1
	1929	12	5	..	
San Bernardino . . . .	1923	13	..	12	
San Diego . . . .	1922	4	..	1	
San Francisco . . . .	1923	2	..	..	1
	1932	8	1	4	
	1921	9	..	8	
San Joaquin . . . .	1931	1	..	1	
	1925	2	1	..	
San Luis Obispo . . . .	1928	11	..	9	
San Mateo . . . .	1932	1	1	..	
	1932	10	3	..	
Santa Clara . . . .	1927	1	..	1	
Sonoma . . . .	1932	3	1	..	
Stanislaus . . . .	1931	2	1	..	
Sutter . . . .	1930	1	..	1	
Tulare . . . .	1926	243	..	..	237
Tahoe District . . . .	1926	3	..	3	
Tuolumne . . . .	1924	4	..	..	

account for the apparent increase of cases in that area." It is to be noted that the high incidence in Marin County, in 1927 and 1929, was due to epidemics in San Quentin prison.

**Case Reports.** CASE 1.—Mrs. C. H. (Kindness of Dr. F. E. Stiles.) A housewife, aged 31, was taken ill on October 30, 1932, with a sudden intense diarrhea, accompanied by fever, abdominal pain and prostration. In 3 days, blood and mucus appeared in the stools. On November 11, 12 days after onset, acute arthritis developed in certain phalanges, later involving ankles, knees and other joints. The arthritis was migratory. Stool culture on November 12 was negative for dysentery bacilli. The blood agglutination was positive for the Shiga group. Stool smears showed excessive pus, mucus, epithelial and cellular elements and debris. On November 6, she contracted an upper respiratory infection, complicated by acute conjunctivitis and iritis. Treatment was symptomatic until November 12, when she received 50 cc. Shiga antiserum intramuscularly, with immediate and permanent cure of the arthritis and residual colitis. Convalescence was uninterrupted and she was dismissed in good health on December 6. The blood count on the 11th day was as follows: Hemoglobin (Sahli), 61 per cent; red cells, 3,150,000; white cells, 12,800; polymorphonuclears, 81 per cent. Urine was normal. The special nurse in charge of the patient showed negative stool culture and agglutination tests.

CASE 2.—Mr. L. H. Teacher, aged 31, son of Mrs. J. H. (Case 3), with whom he made his home, was taken ill 4 days after onset of his mother's illness, with severe diarrhea, lasting 1 week. He did not note the presence of fever. The stools were free of blood. There was no nausea, arthritis or other complication, but considerable abdominal soreness. After 1 week, recovery took place without treatment. He was first seen and examined on the 20th day after onset, and 12 days after cessation of diarrhea. Physical examination was not remarkable. The abdomen was relaxed, and free of tenderness or abnormal masses.

The blood count was as follows: Hemoglobin (Sahli), 79 per cent; red cells, 4,340,000; white cells, 10,480; with polymorphonuclears, 68 per cent; lymphocytes, 24 per cent; mononuclears, 5 per cent; eosinophils, 3 per cent.

Stool culture for dysentery bacillus group was negative. The stools were free of any parasites. Blood gave strong Shiga agglutination reaction.

CASE 3.—Mr. J. H. Housewife, aged 64, began to have diarrhea on November 1, after she had taken care of her daughter for 3 days (Case 1). Two days later, blood appeared in the stools and there was some vomiting. The diarrhea rapidly became dysenteric, was attended by fever, prostration, tenesmus and abdominal pain. Death occurred in shock on November 21.

*Previous history* was of obesity and chronic cholecystitis with stones.

*Examination* showed marked obesity, moderate abdominal tenderness and prostration.

*Laboratory findings* were not available when she was first seen on November 10. At that time, direct inspection of a fresh stool showed little fecal material, large proportion of whitish, translucent flaky mucus giving a milky appearance, much mixed blood, extreme viscosity, and lack of fecal odor. Direct microscopic examination showed enormous numbers of pus cells, macrophages and scattered red cells. This led to a tentative diagnosis of bacillary dysentery. Stool cultures, made at once, were positive for *B. dysenteriae* (Shiga), and there was a Shiga blood agglutination complete at 1 to 40 and partial at 1 to 80. *B. dysenteriae* Hiss-Russell-Y and *B. dysenteriae* Flexner were agglutinated at 1 to 160. Agglutinations were negative for *B. typhosus*, *B. paratyphosus* A and B, *B. enteritidis* and *B. abortus*.

*Treatment* was symptomatic; usual dietary and supportive measures, and colon irrigations with acriflavin. On November 11, 100 cc. Lederle

polyvalent dysentery serum was given in the muscle. On November 14, this was repeated. On November 16, 100 cc. were given in the vein with glucose, and this was repeated on November 17. Glucose was given repeatedly in the vein. On November 20, the patient went into shock, and died on November 21, after a progressive increase of toxemia. Post-mortem examination showed a chronic cholecystitis with numerous stones and a generalized peritonitis. There was extensive ulcerative colitis. Fever chart is appended (Chart I).

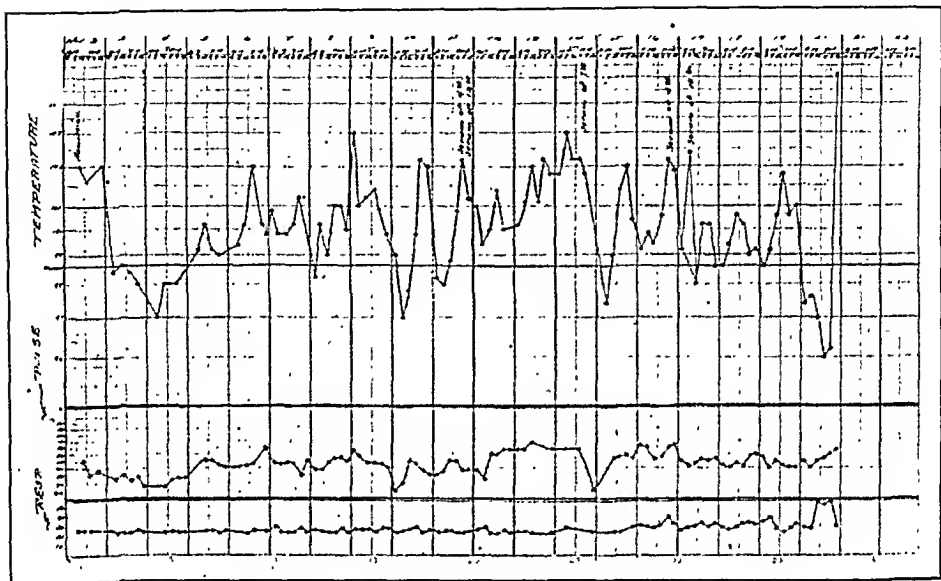


CHART. I.—Temperature chart of bacillary dysentery, Case 3.

**Conclusions.** 1. Bacillary dysentery is widespread in California on an endemic basis, from which institutional and local epidemics easily and frequently arise.

2. Early recognition is necessary for control.

3. Early treatment, especially in severe cases, is essential and demands early diagnosis.

4. Control depends chiefly on personal hygiene, non-infected food handlers and housewives, proper care of clinical cases, clean water supply and safe sewage disposal.

## AGRANULOCYTOSIS AND ACUTE LEUKEMIA.

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ANGINA agranulocytica of Schultz,<sup>1</sup> agranulocytosis of Friedemann,<sup>2</sup> malignant neutropenia of Schilling,<sup>3</sup> pernicious leukopenia of Fitz-Hugh and Krumbhaar<sup>4</sup> and other terms appear to be, to a

superficial observer, antithetic terms to acute leukemia. That is correct if we accept the frequently expressed opinion that agranulocytosis is largely due to an aplastic condition of the bone marrow, whereas the acute leukemia involves a process similar to that of chronic leukemia, but acute in its course. However, this is not the true situation. Let us analyze the two forms in order to find in what points they differ and where they are similar. For agranulocytosis or malignant neutropenia we will indicate a syndrome that by virtue of its fairly constant behavior, although not constituting a definite clinical, pathologic or even hematologic entity, stands out fairly well and is not to be confused with other forms of neutropenia occurring as a temporary picture in a group of well-known diseases, such as typhoid fever, epidemic parotitis, influenza, pappataci fever, Malta fever, pernicious anemia, non-complicated chronic tuberculosis, very severe sepsis and in certain intoxications, such as benzol, gamma rays, mesothorium, Roentgen ray, trinitrotoluol, arsenical compounds, etc. The term acute leukemia is used, as it does not seem necessary to differentiate between myelogenous, lymphatic and monocytic forms. The question of the possible identity of the 3 forms is not relevant to the present topic. We wish also to emphasize that we are considering *manifestations* of the 2 diseases without regard to their bearing on the fundamental nature of the two conditions.

Let us consider the clinical course. It is similar in the two diseases. In both cases we have an obscure insidious onset, although apparently the symptoms develop suddenly. The course of both is characterized by septic manifestations with high fever, ulcerations of the mouth and intestinal tract, and rapidly downward course. Minor differences are found in the duration, which is, as a rule, shorter in single attacks of malignant neutropenia and somewhat longer in the acute leukemia. It is true that from the time that symptoms appear to the date of death, a number of cases of acute leukemia last only few weeks, sometimes a few days; but cases of such short duration are not common and, on the other hand, the blood changes characteristic of the disease may precede the terminal clinical picture for a considerable period of time. Splenic enlargement of moderate size is constant in acute leukemia and usually absent in agranulocytosis. Lymph-node enlargement is also more common in acute leukemia than in agranulocytosis, not taking in consideration the enlargement of cervical lymph nodes, secondary to mouth infection, which is common in both conditions. Another difference is that, whereas profound anemia is always present in acute leukemia, in agranulocytosis it usually develops somewhat later in the course of the disease. A tendency to hemorrhage is present in both conditions. Whereas recovery in acute leukemia is exceptional, a few of the patients of agranulocytosis appear to recover spontaneously. If, however, the cases of severe

neutropenia following the already mentioned intoxications are removed from the list, one will find that spontaneous recoveries from agranulocytosis are indeed rare. Clinically, therefore, it appears that there are no essential differences between the two forms.

Hematologically and pathologically the differences are less than one would imagine. The essential difference which might be suggested by the names and is maintained by some authorities is that in malignant neutropenia the bone marrow is aplastic, whereas in acute leukemia it is hyperplastic. This also is not a real difference, at least in the majority of cases. In several cases of agranulocytosis which I had occasion to see at the autopsy table, the bone marrow was grossly active, or even hyperactive, occasionally hemorrhagic and microscopically showed evidence of active multiplication of cells which showed oxidase granules, although many of them on smear and section did not show any mature granulations. The cells in question were mostly undifferentiated and immature myeloid cells. In fact, the bone marrow examination suggested strongly the picture seen in acute leukemia, the main difference being that, whereas in acute leukemia the undifferentiated cells and immature cells are produced in excess and released in the circulating blood, in agranulocytosis they are retained in the bone marrow. Nor is this the only example of variation in the mechanism of release of immature cells affecting a differentiation between related lesions of the hemopoietic system. Experimentally, Richter and McDowell<sup>5</sup> and Furth and Strumia<sup>6</sup> found that typical lymphatic leukemia, aleukemic leukemia and lymphosarcoma may be obtained in strains of susceptible mice from the inoculation of material from mice affected by chronic lymphoid leukemia, the difference between these forms probably being due to differences in the mechanism of release in the blood of the newly formed lymphocytic cells.

Fitz-Hugh and Krumbhaar<sup>4</sup> speak of a "maturation arrest." These authors noted in a case of agranulocytosis a state of marked hyperplasia of immature myeloid elements of bone marrow. In 2 other cases of agranulocytosis, immature myeloid cells were present in the bone marrow in increased numbers. These authors also emphasize the necessity of considering the bone marrow condition for the proper interpretation of the neutropenic state, and mention the similarities to pernicious anemia.

Custer<sup>7</sup> thus expresses himself: "I believe that one should differentiate strictly between those neutropenias of secondary nature (symptomatic agranulocytosis) and those of the primary type (essential agranulocytosis, Schultz's syndrome), both on clinical and histopathologic grounds. With regard to the latter, I have found in all cases that fit the clinical features of the primary type a rather consistent bone marrow picture. The marrow is always hyperplastic, the degree depending on the duration of illness; the increase in cellularity is largely confined to the granulocyte progenitors,

shared to slight degree by the erythropoietic series. More specifically, the hyperplasia is of myeloblasts and promyelocytes; rarely is a fully granulated neutrophilic myelocyte found (in 1 case I searched through many sections of 5 bones without finding a single granulated cell of the neutrophil type). Beyond the promyelocyte, one finds degenerating forms (ghost cells) that from their nuclear remnants are often identified as belonging to the series in question. Some of the cases show focal areas of necrosis, in the periphery of which there is a lymphocyte and plasmocyte reaction, sometimes extensive enough to completely cover the necrotic center."

Anatomically, from an examination of a large number of autopsies, I have constantly found in the bone marrow of acute leukemia a picture very similar indeed, although, as a rule, more severe than that found in agranulocytosis. The fundamental difference is that, whereas in agranulocytosis there is an arrest of maturation of cells without release of these cells in the circulating blood, in acute leukemia these immature cells are released into the blood. This difference might be minimized if one considers that in agranulocytosis one always finds in circulation a small number of highly immature granulocytic cells and that a large number of shadow cells occur in both diseases. Another important difference, possibly related to the previous one, is that, whereas in acute leukemia there are foci of cellular infiltration in other organs of the body, in agranulocytosis one does not find such foci. In both diseases there is a constant severe deficiency of mature granulocytic cells in circulation. This deficiency is never present in chronic myelogenous leukemia, and in chronic lymphatic leukemia it occurs only occasionally in the very last period of the disease. Essentially, therefore, in both agranulocytosis and acute leukemia the clinical manifestations of sepsis are probably secondary to a disappearance of the protective function of the neutrophilic cells from the circulating blood. Another strong point of resemblance is that, in both agranulocytosis and acute leukemia, degenerative lesions of the bone marrow occur very commonly. Finally, I will mention the fact that, in a number of cases of acute leukemia, the typical hematologic picture is preceded by a picture of neutropenia.

The purpose of this paper is to present 3 cases of acute blood dyscrasias that presented at one period or another of their course alternatively the hematologic features of acute leukemia and those of agranulocytosis. Schenck and Pepper<sup>8</sup> seem to have been dealing with a similar case in their presentation in 1926 of a case of acute lymphoblastic leukemia with remission characterized by neutropenia. These authors remark on the confusion in differential diagnosis between acute leukemia and infectious mononucleosis. This confusion is partly due to the chaotic nomenclature of blood cells, but much more so to the improper knowledge of blood morphology on the part of those who examine the blood films. I have



for many years adopted, with minor modifications, Ferrata's<sup>14</sup> blood-cell classification and nomenclature, which is similar to that of Pappenheim, and consider it one of the most satisfactory. Borehard,<sup>9</sup> in 1930, presented a case of agranulocytosis in a female patient in which the picture changed to a typical form of acute myeloblastic leukemia followed by death. Lindemann,<sup>10</sup> in 1930, emphasized the similarity between 3 cases, 1 of glandular fever with mouth infection and recovery, 1 of typical acute lymphatic leukemia, with death, and 1 of severe agranulocytosis, also terminating in death. In 1931, Wolff<sup>11</sup> reported 2 fatal cases in a brother and sister, 1 of agranulocytosis, the other of myeloblastic leukemia, as forms of reaction to the same infection. Such cases appear to support the thought that in both forms we are perhaps dealing with a pre-existing congenital or acquired deficiency of the bone marrow, combined with an intercurrent non-specific toxemia, probably infectious, or perhaps with a phenomenon of a hypersensitivity to certain substances. Wolff concludes from his own cases, and from the literature reports, that agranulocytosis, aplastic anemia, aleukia (Frank) and the acute leukemias do not constitute independent diseases, but represent abnormal reactions to a septic infection, based upon a constitutional inferiority of the blood organs. Burkens,<sup>12</sup> in 1931, reported a fatal case of agranulocytosis followed by acute leukemia in a girl, aged 16, the attack of acute lymphatic leukemia occurring 1 year after the attack of agranulocytosis. He speaks similarly of constitutional inferiority of the regulating mechanism of hemopoiesis, revealing itself first with an agranulocytic picture and later with a fatal acute leukemia. More recently, Fitz-Hugh and Comroe,<sup>13</sup> reviewing 18 cases of agranulocytosis, report that necropsy study in 9 cases has shown in 6 moderate or intense hyperplasia of the immature myeloid elements, in 2 a normal picture and in only 1 (a case not examined by the authors) scarcity of myeloid elements. Müller and Spröhnle<sup>15</sup> described a case of hypochromic anemia and leukopenia with few immature leukocytes in the circulating blood in which suddenly a typical picture of acute leukemia appeared.

**Case Reports.** CASE 1.—J. T., a white male, aged 21, was admitted to the Misericordia Hospital on August 17, 1931 (service of Dr. J. A. Sweeney). About 10 weeks previously he first complained of shortness of breath on exertion and pains in the back. Two weeks prior to admission, dizziness and headache appeared. Three days before admission, a tooth abscess developed. On admission the patient showed paleness of skin and mucosa, few petechiae over the abdomen and left arm, moderate enlargement of the cervical, axillary and inguinal lymph nodes, slight enlargement of the spleen which was palpable below the costal margin, slight oozing of blood from the gums with stomatitis and a suppurative process about the lower right 1st and 2d molars with a fistula; a blowing systolic murmur of the heart. The temperature was irregular, subfebrile most of the time, with a maximum of 103° F. The blood examination on admission showed: coagulation time, 4½ min.; bleeding time, 6½ min.; hemoglobin, 3.35 gm.;

erythrocytes, 1,160,000; leukocytes, 36,300. The differential count showed: hemocytoblasts and hemohistioblasts (undifferentiated cells), 84%; promyelocytes, 2; metamyelocytes, 1; prolymphocytes, 3; lymphocytes, 7; Türk cells, 3%. A large percentage of the undifferentiated cells showed oxidase granules. The diagnosis of acute leukemia of the myelogenous type appears well justified.

The clinical condition and leukocytic picture went on almost unchanged, save for variation in the number of the leukocytes, from a minimum of 6700 to a maximum of 72,000, for a little over a month. During this period the patient received repeated blood transfusions at fairly even intervals which did not apparently alter either the course or the blood picture. At the end of this period, or about September 15, the leukocytes in the circulating blood rapidly declined in number until they reached figures below 1000 per cmm. Along with the drop in the total white cell count a very interesting change took place in the leukocytic formula, that is, the progressive disappearance of the myeloid elements, both mature and immature. The blood picture on October 5 is typical of the agranulocytic period: hemoglobin, 7.3 gm.; erythrocytes, 1,960,000; leukocytes, 550. Differential count: hemohistioblasts, 1%; rod nuclears, 1; neutrophils, 1; prolymphocytes, 3; lymphocytes, 94%. This granulopenic phase went on for about 1 month. During this period the leukocytes were as low as 400 per cmm. and seldom above 1000. The anemia improved somewhat, and so did the clinical condition of the patient. About November 3, the undifferentiated myeloid cells reappeared in the blood stream, and in 3 weeks, from a count of 2100 leukocytes per cmm., a maximum of 430,000 was reached.

The blood picture at the end of the disease (November 18) was again that of a typical acute leukemia with 240,000 leukocytes and the following differential count: hemohistioblasts and hemocytoblasts (undifferentiated cells), 41%; myeloblasts, 40; promyelocytes, 4; myelocytes, 1; polymorphonuclears, 2; lymphoblasts, 3; lymphocytes, 5; Türk cells, 2; undetermined, 2%. It is interesting to note that at this stage few of the undifferentiated cells were oxidase positive, although many were unquestionably of myeloblastic nature. This phenomenon has been observed by me in other cases of acute myelogenous leukemia. Under such conditions, even typical neutrophils do not show oxidase granules. During the whole course of the disease, the platelets were very low, varying between 25,000 and 70,000. During the last few days of life an autoagglutination of the red cells *in vitro* took place, rendering red cell counts impossible.

An analysis of the behavior of the differential count shows that with the decrease of the undifferentiated cells there is a sharp increase, first of the immature granulocytes, then of the mature granulocytes, as if the maturation of these cells had become progressively possible for a short period of time. The same phenomenon occurred, but reversed and somewhat less strikingly during the reappearance of the undifferentiated cells. The patient died with symptoms of cerebral hemorrhage on November 20, about 5½ months after the onset of the first symptoms and about 3 months after the disease was diagnosed. Chart I summarizes the variations of the hematologic picture.

CASE SUMMARY. We have, therefore, a case of acute leukemia of the myelogenous type, with a period of leukopenia and granulopenia lasting over a month, with clinical improvement, followed by a rapid and fatal return of the leukemic picture.

CASE 2.—E. Y., a school girl, aged 9, was first seen by me on October 18, 1927, the history being that from March the child had noticed petechiae all over the body and black and blue marks after slight injuries. About May, bleeding from the nose occurred. During this period the patient had been treated with repeated blood transfusions. There had been all

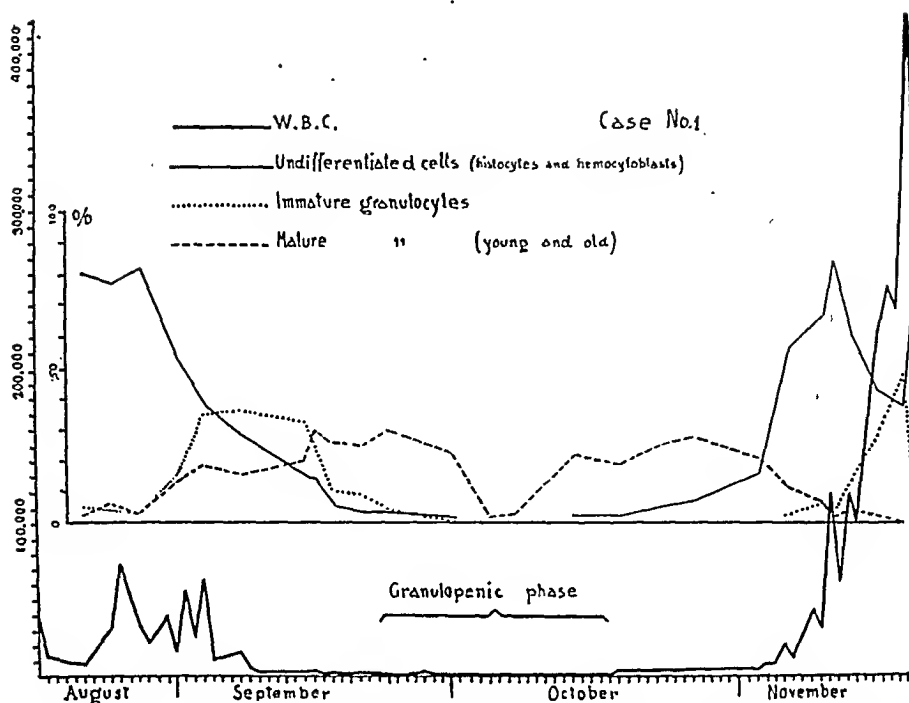


CHART I.—Note the typical picture of acute leukemia (granulocytic) at the beginning and end of diseases, with a striking intermediate granulopenic phase.

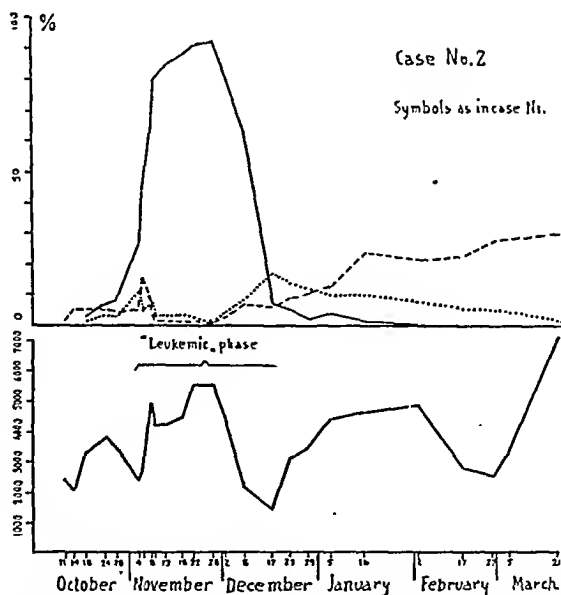


CHART II.—An early granulopenic phase is followed by a typical acute leukemic picture (lymphoblastic). This is followed by a second neutropenic phase from which the patient slowly improves.

along a severe mouth infection which in July rapidly spread with formation of fetid sores all over the mouth and finally sloughing of 1 tonsil. The temperature had been intermittently high. The hemoglobin content, the red cells and the platelet count were constantly low. On October 11 the blood examination showed bleeding time of over 15 min., coagulation time 4 min.; platelets, 33,000; hemoglobin, 9.2 gm.; red blood cells, 1,785,000; white blood cells, 2400; neutrophils, 1%; basophils, 2; prolymphocytes, 4; lymphocytes, 92; monocytes, 1%—a picture, therefore, of anemia and leukopenia with great decrease in the total number of granulocytic cells, but practically no change in the lymphocytic series. The diagnosis of agranulocytosis was made.

On or about November 4, a distinct change occurred in the differential count. There was a rapid and continuous increase in the number of the undifferentiated cells which finally reached the total figures of over 90%. There was at the same time a slight increase of the total white cell count. This phase, having hematologically all the characteristics of an acute leukemia, lasted about 1 month. During the acme of this period, on December 28, the differential count showed 92% hemocytoblasts, 1% promyelocytes, 1% rod nuclears (young neutrophils) and 6% lymphocytes, with a total leukocyte count of 5600. The undifferentiated cells at the end of the leukemic period disappeared as rapidly as they had appeared, and there was again a picture of leukopenia with granulopenia which, however, began slowly to improve (Chart II). The improvement extended over a period of 3 years. The patient was treated with a very large number of blood transfusions and injections of fresh serum. The child is at present living and apparently well, but still has a low white cell count, ranging from 4000 to 5000, with a relative lymphocytosis and a mild absolute granulopenia. From the table it can be seen that during the period of increase and decrease of the undifferentiated cells, an increase of both mature and immature granulocytic cells occurred. The majority of the undifferentiated cells (hemocytoblasts) showed positive oxidase reaction.

**CASE SUMMARY.** The second case shows a rather long-standing granulopenia with a sudden change of the blood picture to one of acute leukemia of the myelogenous type. This picture lasted about 1 month and eventually disappeared, the agranulocytic picture then returning, and the patient slowly improved. The improvement has lasted during the period of observation up to date.

**CASE 3.**—Z. F., a white male, aged 5, first came to my observation on October 20, 1931. The child had been ill for about 1 month, with irregular high fever, abdominal pains, diarrhea with bloody stools and mucus. On the first examination, the child showed pallor, temperature ranging from 103° to 104° F. with daily remissions, diffuse mouth infection, rapid pulse, a systolic murmur and muffled heart sounds. Hospitalization for study was advised, and on November 7 the child was admitted to the Pediatric Service of the Mt. Sinai Hospital (Dr. Harry Lowenburg). The physical condition at the time of admission had not changed considerably since the previous examination. In addition the lips were swollen, fissured and bleeding. The posterior cervical glands were larger than normal and tender to the touch. The lungs were impaired at both bases with fine crackling râles. The Roentgen ray showed marked infiltration suggesting bronchopneumonia and evidence of pericardial effusion. The systolic murmur was still present, but disappeared 10 days later, and the heart sounds became more distinct. The child was treated with 4 blood transfusions and discharged improved on December 3, 1931. The temperature had been between 99° and 105° F. for several days, finally returning to normal. Smears from the gums showed many fusiform bacilli.

The patient was readmitted to the same institution 2 weeks later with fever and generalized lymphadenitis and enlargement of liver and spleen. Splenectomy was performed on January 21, 1932. The spleen weighed 500 gm., was moderately firm, deep purplish red in color with hyperplastic lymph follicles and a slightly thickened capsule. Microscopic examination gave the following result: The capsule was well preserved, normal in thickness. Outside of the capsule and adherent to it there was a thin layer of lymphocytic cells appearing in groups that continued to the spleen pedicle. Here the capsule appeared to be thoroughly infiltrated by lymphocytic cells. These lymphocytic cells, which form the bulk of the splenic tissue, were larger than the ordinary lymphocytes, the nuclear structure was much more delicate than that of the mature lymphocyte; they showed a number of nucleoli. The cytoplasm was relatively scanty and basophilic. These cells showed very numerous mitotic figures, and formed irregular, compact areas with almost complete loss of the normal splenic structure. There were a few well-preserved lymph follicles, which were, however, very greatly hyperplastic. This picture was in sharp contrast with that of chronic lymphatic leukemia, where the prevailing cell is the prolymphocyte (a small lymphocyte with a compact, very dark staining nucleus). The cell prevailing in the sections can be identified either with the lymphoblast or with the lymphoid hemocytoblast. It is the picture of an acute leukemia and not the picture of a chronic lymphatic leukemia. It is of very great interest to note that, although the picture offered by the spleen was surely that of acute leukemia, the typical leukemic changes in the blood were not as yet established and did not definitely appear until several weeks later. A similar behavior was found by Furth and Strumia<sup>6</sup> in susceptible mice inoculated with material from leukemic animals.

The temperature at this time was irregular, with febrile periods. The patient received numerous blood transfusions and was discharged on March 18, 1932. He was readmitted on April 4, when new glandular enlargement was detected in the axilla and in the groin. Child had at this time a septic temperature with elevations up to 105° F. He was treated again with repeated blood transfusions and discharged on April 15. The blood picture at this time was typically that of an acute lymphocytic leukemia.

After a period of 4 weeks of relative improvement at the Convalescent Home he was readmitted to the hospital for blood transfusion. During this period the temperature varied between 98° and 104° F., finally remaining normal for 4 days. He was discharged, only to be readmitted 4 days later because of distention of the abdomen and severe pains in the right upper quadrant. His temperature on this last admission was 100° F., and the liver larger than on previous occasions. Adenopathy was still present. A bilateral parotitis developed, with some bleeding from the mucous membrane of the lips and the left cheek. The temperature now varied between 98° and 105° F. The child died on July 5, 1932.

**CLINICAL SUMMARY.** A five-year-old child acutely ill with septic temperature, generalized adenopathy, enlargement of the liver and spleen, mouth infection, occasional bleeding and occasional intercurrent infections of various organs (lungs, pericardium, parotid glands, intestinal canal). The blood picture is summarized in Table 1. In addition it should be stated that on several occasions there had been a moderately low platelet count (190,000 and less). The course of the disease could roughly be divided into 3 periods: The infectious period, from the time of the first observation up to about December 16; the granulopenic phase, from December 16 to about January 15; and thereafter to the end, the progressive leukemic phase.

The rapid course of the disease, the septic character, the relatively low

white cell count, with a large percentage of undifferentiated or highly immature cells during the leukemic period, fully justified the diagnosis of acute leukemia of the lymphocytic type. The oxidase stains done on several occasions always showed that the undifferentiated cells were oxidase negative.

*The autopsy* (Dr. D. Meranze) fully confirmed the diagnosis of acute leukemia. The body showed considerable emaciation. All lymph nodes of the body were greatly enlarged, particularly in the mediastinum, near the pancreas, and the mesentery. The lymph nodes appeared soft, fleshy, often hemorrhagic. Hemorrhages were present over the pericardium, in the liver, the kidneys, the stomach. Gross leukemic infiltration was present in the left kidney, which was greatly enlarged and weighed 140 gm. The bone marrow (femur) was hyperplastic. Microscopic examination (Strumia) showed:

*Bone Marrow.* Distinct hemopoietic hyperplasia, with very great reduction in number of mature granulocytic cells. There were very few erythro-

TABLE 1.—BLOOD FINDINGS IN CASE 3.

	October 20, 1931.	November 16, 1931.	March 7, 1932.	May 9, 1932.	June 7, 1932.
Hemoglobin (grams) . . .	7.1	10.5	10.0	3.0	2.5
Red blood cells . . .	2,500,000	3,070,000	2,520,000	1,090,000	880,000
White blood cells . . .	4,800	3,200	20,800	71,300	4,500
Hemohistioblasts . . .	....	....	....	0.6	....
Hemoctyoblasts . . .	....	....	1	0.4	13.5
Myeloblasts . . .	....	1	....	....	0.5
Promyelocytes . . .	....	2	....	0.2	....
Myelocytes . . .	....	1	....	....	....
Metamyelocytes . . .	1	4	....	....	....
Rod-nuclears . . .	5	22	2	....	1.0
Neutrophilic polys. . .	1	20	2	0.2	0.5
Eosinophils . . .	....	....	....	....	....
Basophils . . .	....	1	....	....	....
Lymphoblasts . . .	1	....	16	7.2	36.5
Polymorphocytes . . .	5	17	14	90.4	28.0
Lymphocytes . . .	87	32	65	0.8	12.0
Monocytes . . .	....	....	....	....	0.5
Erythroblasts basophilic . . .	....	....	....	....	1.5
Erythroblasts metachromatic . . .	....	....	....	....	5.5
Erythroblasts eosinophilic . . .	....	....	....	....	0.5

blastic foci. Most of the cells were large cells with relatively scanty cytoplasm, large vesicular nucleus with fine structure, basophilic cytoplasm and no granulations. Megakarocytes were very rare. Occasional edema. There were numerous mitotic figures and fairly numerous large cells fitting well the description of hemohistioblasts. Oxidase stain not carried out. The lesion could be summarized by saying that there was a distinct hyperplasia, with lack of mature myeloid cells, erythroblastic foci and megakaryocytes. The predominating cells were undifferentiated, very similar to those found infiltrating the other organs.

*Lymph Nodes.* The structure of the lymph node was entirely lost. There were extensive areas of hemorrhagic infiltration. The bulk of the tissue was formed of loose fibrillar tissue thoroughly infiltrated with relatively large cells, with basophilic cytoplasm. These cells appeared to be

of two distinct types. There were some with very scanty cytoplasm, compact, heavy stained nucleus with little or no structure (prolymphocytes). There were also a number of cells with more abundant cytoplasm, large vesicular nuclei, with a rather delicate structure and occasional nucleoli (lymphoblasts).

*Liver.* The liver tissue proper showed degenerative changes with granulation of the cell cytoplasm and generally poor nuclear stain. There was some dilatation of the central veins and surrounding capillaries with a small amount of hemosiderin deposit. The outstanding lesion, however, was the presence of bulky thick cellular infiltration which occurred regularly in the periphery of the lobules. The cellular infiltration was made up of cells mostly of the lymphocytic type, of the same two kinds as in the lymph nodes. Diagnosis: leukemic infiltration.

*Kidney.* Most glomeruli showed in the capsular space extensive serous exudate in the form of granular pink staining material. The tubular epithelium showed extensive degenerative process, the lumen being filled with the same granular material already mentioned. In addition there was extensive cellular infiltration, which occurred sometimes around the glomeruli, sometimes around and between the tubules. It was formed of lymphocytic cells, identical to those already described for other organs. There were also small areas of hemorrhages. Diagnosis: parenchymatous nephrosis; leukemic infiltration.

**CASE SUMMARY.** This case, somewhat more complex than the previous ones, is of very great interest because it shows a typical infectious picture with progressive depression of the granulocytic activity followed by an abnormal regeneration of the lymphocytic cells, with appearance in the circulation of a large number of undifferentiated and highly immature cells, and a typical clinical and postmortem picture of acute leukemia.

**Summary and Conclusions.** Evidence gathered from the clinical course, the hematologic picture and the anatomic lesions of the 2 diseases point to many similarities between agranulocytosis and acute leukemia. These similarities are made more striking by at least 6 reported cases of transition of one form into the other, 3 of which are presented in this paper. The essential disturbance dominating both pictures seems to be a defect in the bone marrow, whereby the immature parent cells become incapable of maturation, a disturbance perhaps based on a constitutional imperfection of the hemopoietic system, congenital or acquired, in both cases. The rôle played by intercurrent infections, toxemias or susceptibility to various substances may be the deciding factor in the development of the acute picture, though not necessarily a specific one. An essential difference between the 2 forms seems to be in the mechanism of release of the immature and undifferentiated cells into the circulating blood, a release which occurs in acute leukemias, but not in agranulocytosis.

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## NEUTROPENIA DEVELOPING DURING AMIDOPYRIN MEDICATION.

### WITH REPORT OF 2 CASES.

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AMIDOPYRIN has been used extensively in this clinic as an analgesic in the treatment of chronic arthritis. Schultz<sup>1</sup> reported that the drug had little, if any, toxicity; but 2 of the patients in our series developed neutropenia while taking it. In 1 case the association seems definite while, in the other, the relationship is suggestive but not conclusive. We were unable to find reference in the literature to the neutropenogenic action of amidopyrin. Hence the 2 following case reports:

CASE 1.—A. M., white male, 48, admitted May 13, 1933. Had arthritis about 5 years. Ten months previous to admission two infected teeth were extracted and the tonsils were removed. The blood Wassermann reaction was negative. The remainder of the history and physical examination were unimportant. The blood count on admission was: R. B. C. 4,250,000, W. B. C. 10,000, polys. 68, lymph. 22, mono. 4, eos. 6%. Beginning May 13, 3 tablets each consisting of a combination of magnesium carbonate gr. iv and amidopyrin gr. iiss, were given daily until May 23. The dose was then increased to 4 tablets daily until June 6, when it was discontinued. The blood count was normal at that time. On June 10, amidopyrin gr. xv was given daily until June 17 when it was increased to gr. xx daily. This dose was continued until June 26 (a total of 285 gr. in 16 days) when the neutropenia was discovered (Table 1). At the time of the neutropenia, the patient felt quite well. There was no sore throat and no untoward symptoms were observed. The blood count, which was taken daily, returned to normal in 9 days. During this interval, the sole treatment was omission of the amidopyrin.

After 32 days without medication (Aug. 8) it was again given in daily doses of gr. xx for 14 days (a total of 280 gr.). The neutropenia then reappeared, as shown in Table 1. Other signs and symptoms were also present and the patient complained of malaise, headache, general body aches and a poor appetite, but these appeared 24 hr. after the neutropenia was discov-



ered. The next day there was a sudden attack of nausea, vomiting, hypogastric pain, chills and the temperature rose to 102°. The W. B. C. were 3800 with 2% polys. At this point we were afraid that simply abstaining from the amidopyrin would not be sufficient to eliminate the neutropenia, and pentnucleotid was given intramuscularly and glucose solution intravenously. Within 9 days after the omission of the drug, the blood count was again normal and has remained normal to date. There was no sore throat at any time.

TABLE 1.—BLOOD COUNTS OF CASE 1.

Date.	R. B. C. in millions.	W. B. C. in thousands.	Differential.						
			Polys.	Lymph.	Mono.	Eosino.	Baso.	Myelo.	Pre- myelo.
5-13-1933	4.25	10.0	68	22	4	6	0	0	0
5-17-	...	12.4	64	28	4	6	0	0	0
6- 6-	5.2	11.5	60	32	6	2	0	0	0
6-16-	5.4	11.8	68	30	2	0	0	0	0
6-26-	5.07	4.0	2	56	8	6	2	26	0
6-27-	...	4.1	3	57	2	11	2	23	2
6-28-	5.15	5.8	12	63	2	6	0	17	0
6-29-A.M.	5.45	6.4	15	47	2	13	1	22	0
6-29-P.M.	5.45	6.3	27	53	1	3	0	16	0
7- 1-	...	7.0	26	47	7	7	1	12	0
7- 3-	4.61	10.8	47	41	3	6	1	2	0
7- 5-	4.80	12.5	60	34	4	0	0	2	0
7- 6-	5.20	11.9	65	27	3	2	0	3	0
7-22-	...	11.0	64	28	6	2	0	0	0
8- 2-	...	10.8	59	33	4	4	0	0	0
8-12-	5.00	11.4	66	24	6	2	2	0	0
8-15-	5.50	10.7	60	30	8	2	0	0	0
8-17-	5.35	10.4	56	36	2	6	0	0	0
8-21-	...	6.3	27	42	2	3	0	26	0
8-22-A.M.	...	4.0	6	45	4	6	0	37	0
8-22-P.M.	...	3.8	2	38	4	6	0	50	0
8-24-A.M.	4.14	5.3	11	39	0	0	0	50	0
8-24-P.M.	...	8.4	26	39	1	3	1	30	0
8-25-A.M.	...	7.8	39	36	1	6	1	17	0
8-25-P.M.	...	7.8	33	35	3	4	0	25	0
8-26-A.M.	...	10.1	48	29	5	6	0	12	0
8-26-P.M.	...	9.0	42	40	0	8	0	10	0
8-29-	...	7.5	62	24	1	0	0	10	0
8-30-	...	11.1	70	18	0	2	0	10	0
8-31-	...	11.4	62	27	0	4	0	0	0
9- 5-	...	9.5	74	23	1	2	0	0	0
9-11-	4.3	10.7	64	27	3	3	0	3	0

CASE 2.—Mrs. R. P., Italian, aged 33, admitted December 3, 1932, complained of swelling and pain in the fingers of both hands and pain in both knees of 2 months' duration. Past history was unimportant except for cholecystectomy in 1927. The blood count on admission was: R. B. C. 3,800,000, W. B. C. 6200, polys. 56, lymph. 44%. The blood Wassermann reaction was negative. On Jan. 7, 1933, 4 tablets each consisting of a combination of magnesium carbonate gr. iv and amidopyrin gr. iiss were given daily. This was continued until Jan. 20 (13 days) when the medication was increased to 5 tablets daily. On Feb. 4 the patient complained of occasional headaches with some nausea but no vomiting. The W. B. C. was 5000 with 30% polys. The medication was discontinued. She had received a total of 275 gr. of amidopyrin in 28 days. The largest daily dose was gr. xiiss. On Feb. 6 the W. B. C. were 3000 with 2% polys. We did not see the patient again but her family physician stated that on Feb. 7, 24 hr. later, she developed an acute sore throat with edema, pyrexia and nausea and vomiting.

On Feb. 10 she was admitted to the Willard Parker Hospital in an extremely prostrated and semicomatose condition. The temperature was 106.8°. A laryngoscopic examination revealed an ulceration of the left

side of the pharynx which extended down to the epiglottic and arytenoid regions—the mucosa appearing black-purple, with many petechiæ. The epiglottis was very edematous and angry red. The posterior arytenoid portion was greatly swollen and red and obscured the glottis. The W. B. C. were 500 with no polys. She was given a transfusion but failed rapidly and died 12 hr. after admission.

**AUTOPSY.\*** A marked edema, almost a cellulitis of the neck: a marked congestion throughout both lungs; and the heart showed petechial hemorrhages on the left auriculoventricular juncture. The local lesions in the buccal cavity showed a moderate edema and thickening of the base of the tongue and an ulcerated area over the left tonsillar region extending down to the posterior pharyngeal wall to involve the arytenoid fold. The entire epiglottis was moderately edematous but the glottis on the left was so edematous as to extend beyond the midline on the right. The larynx, similarly, showed marked edema of the cords and the tracheal mucosa, likewise, showed moderate edema and congestion.

The *liver* was moderately congested and showed a considerable yellowish discoloration with evidence of fatty degeneration. There was no apparent bile stasis and no cirrhosis.

The *spleen* was purplish-red in color and the capsule was tense. On section, there was obvious acute congestion. The normal architecture was rather obscured and there were no discernible follicles. The medullæ of the *adrenals* were somewhat thicker than the average and rather hemorrhagic in appearance. The *thymus* was persistent but of normal appearance. The *lymph nodes* in the cervical region, around the trachea and at the bifurcation of the primary bronchi, were extremely large, dirty grayish-red in color and on section some showed an acute necrosis with pus formation. *Anatomical diagnoses:* Acute ulcerative arytenoiditis; acute edema of the epiglottis, glottis and larynx; agranulocytosis; persistent thymus.

**MICROSCOPIC EXAMINATION.** *Heart.* A marked interstitial edema with moderate congestion, which seemed to be a part of the acute process and an interstitial cellular infiltration, entirely monocytic in character, was present.

*Liver.* There was moderate congestion of the sinuses, particularly in the central areas, with an almost complete absence of white cells in the sinuses. Many of the nuclei centrally showed marked hyperplasia suggesting the possibility of previous central necrosis with regeneration.

The portal areas showed slight monocytic cell infiltration around the bile ducts.

*Spleen.* There was extreme congestion and the follicles were prominent and numerous but of average size. There was very little activity in their germinal centers. There was a diffuse reticulo-endothelial hyperplasia with connective tissue increase of the stroma. No granulocytes were noted in the congested pulp.

*Adrenals.* There was a moderate congestion with more fatty vacuolization than normal in the cortical cells.

*Organs of the Neck.* Sections from the ulcerative area of the throat and the adjacent tissues presented evidence of an extreme degree of edema. This extended into the musculature widely separating the muscle fibers, many of which showed extensive degeneration. There was a diffuse bacterial invasion of the tissues, mostly streptococcal, but there was a complete absence of cellular infiltration except a few scattered lymphocytes and large mononuclear phagocytes.

*Bone Marrow.* Sections from the femur showed many clumps of reticulo-endothelial cells and lymphocytes and plasma cells and islands of red-cell

\* We are indebted to Dr. Lawrence W. Smith and the authorities of the Willard Parker Hospital, Department of Hospitals, New York City, for the autopsy report.

activity were present. Megakaryocytes were present in moderate numbers and a few early myeloid cells, chiefly undifferentiated, were noted. Essentially, there was no myeloid activity. These changes were similar in the marrow from the vertebral column and ribs but there were more early myeloid cells in the vertebrae.

**Discussion.** Two instances of neutropenia developing while the patients were receiving amidopyrin are presented. Patient 1, returned to normal 9 days after the drug was omitted, without any other form of treatment. After a period of rest the amidopyrin was resumed. This was followed by neutropenia after the patient had received about the same amount of the drug as on the previous occasion (280 gr.). The W. B. C. returned to normal in 8 days or about the same time as after the first attack. The rapid recovery after the omission of the drug, in one instance without therapy and in the other with only 4 injections of 10 cc. each of pentnucleotid would seem to indicate that the neutropenia was probably produced by the amidopyrin. The second fatal case was the first instance of this phenomenon observed in the clinic and at that time we were uncertain as to whether amidopyrin played a part in its etiology. In the light of our recent experience we feel certain it was caused by the amidopyrin. Although the second patient was taking a combination of magnesium carbonate and amidopyrin, the fact that Patient 1 developed two attacks of neutropenia after the use of amidopyrin alone, we believe, eliminates any probability that magnesium might have played any part in the condition. A predisposition to neutropenia may have existed in these patients or the onset may have been due to the inability of the bone marrow to cope with any additional strain which may have been brought on by the amidopyrin. Neutropenia is frequently periodic in character and may be produced by several factors as pointed out by Beck.<sup>2</sup> Farley<sup>3</sup> reviewed 39 cases appearing in the literature in which the function of the bone marrow was depressed following the use of various preparations of arsphenamin. Taking these into consideration and recognizing that benzene is a powerful leukocytic depressant, it is possible that amidopyrin, a benzene derivative, could be an etiologic factor.

The above 2 cases occurred in a series of 200 patients receiving the drug. In 2 other patients, the poly. counts were reduced from 55 and 60% to 35 and 40% respectively while taking amidopyrin, but the poly. counts promptly returned to normal when the drug was omitted. Two others in the series developed nausea, vomiting, exhaustion, pyrexia, etc., but blood counts were not obtained. It is possible that these cases may have been similar to the 2 cases detailed above and that they may have made spontaneous recovery when the drug was omitted.

**Conclusions.** 1. Evidence is presented that 2 patients and possibly 4 others developed neutropenia while taking amidopyrin.

2. It is suggested that the adoption of periodic blood counts in patients receiving amidopyrin may prevent the onset of this syndrome.

3. The drug should be temporarily discontinued following symptoms suggestive of intoxication.

I wish to express my thanks to Dr. A. S. Price, pathologist of the hospital, for his cooperation in studying the hematology of these cases.

NOTE.—Since this paper was submitted the following articles have appeared: Watkins, C. H. (The Possible Role of Barbiturate and Amidopyrin in the Causation of Leukopenic States, *Proc. Staff Mayo Clinic*, 8, 713, 1933), reported 32 cases of granulocytopenia. Amidopyrin was responsible for 10 cases, 2 of which were fatal. Two cases were considered due to amidopyrin plus diallyl barbituric acid, but no deaths occurred. Five fatal cases were attributed to isoamyl-ethyl-barbituric acid. F. W. Madison and T. L. Squier (The Etiology of Primary Granulocytopenia [Agranulocytic Angina], *J. Am. Med. Assn.*, 102, 755, 1934) studied 14 patients, each of whom had taken drugs containing amidopyrin either alone or in combination with a barbiturate. Except in the severe cases, the patients recovered, when the drug was discontinued. An additional case with fatal termination has been brought to my attention through the courtesy of Dr. C. W. Lieb (personal communication). M. C., aged 78, had osteoarthritis of 6 months' duration. She had been taking 5 gr. of amidopyrin daily for 2 months. The blood count at that time was normal. The following month she had taken 10 gr. of amidopyrin daily. After the third week of this medication she came under Dr. Lieb's care. The blood count was: white blood cells 240, with no neutrophils and 10% monocytes. Highly toxic strains of *S. aureus* were isolated from postnasal cultures and toxic streptococci were recovered from the throat. She was given 3 transfusions, pentnucleotid and liver extract without effect on the blood count.

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## A NOMOGRAPH FOR SIMPLIFYING COMPUTATION OF THE URINE SEDIMENT COUNT (ADDIS).\*

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It is the experience of many that the most difficult part of the urine sediment count of Addis<sup>1</sup> is the computation of the results rather than the making of the count itself. In an effort to lessen this labor the accompanying nomograph was devised.

In the sediment count computation is required for the determination of five quantities: (1) the 12-hour volume of urine; (2) the total protein excretion; (3) the cast count; (4) the red cell count, and (5) the white and epithelial cell count. The raw data on which these computations are based include: (1) the period of time over which the urine is collected; (2) the volume of the voided urine; (3) the volume in which the sediment is mixed; (4) the numbers of

\* Supported, in part, by a grant from the Rockefeller Fluid Research Fund of the School of Medicine, Stanford University.

each of the formed elements counted per unit volume of counting chamber, and (5) the volume of protein precipitate.

The nomograph consists of scales representing the above variables, constructed in such a way that any straight line intersects related scales at corresponding points. For example, the 12-hour urine volume depends on the volume of urine voided and the period over which it is collected. If a convenient form of straight line such as a taut thread be placed across Scales A and B intersecting them at points corresponding to the last two variables above, the straight line will be found to intersect Scale C at a point giving the 12-hour volume. This procedure is repeated, combining various scales to compute various data.

The scales of the nomograph are logarithmic and consequently non-uniform. They are used in alphabetical order, A and B being combined to give a reading on C, C and D together giving a reading on E, and E and F giving values on G. A time-saving exception to this order is to compute the protein excretion (by means of Scales C, J and K) immediately after C is determined and before going on to D and E. With reasonably careful setting and reading of the values on the nomographic chart of size  $8\frac{1}{2}$  by 11 inches,\* the mathematical error will be less than 5 per cent, a departure which is well within the limit of the method.

The scales for calculation of the protein excretion apply to Dr. Addis' modification of the technique of Shevky and Stafford,<sup>2</sup> from which it differs only in the use of graduated centrifuge tubes of 6.5-cc. instead of 13-cc. capacity. With the 13-cc. tube the result obtained from the nomograph is divided by 2.

The counts are made in the ordinary blood counting chamber, each of the two sections of which has a ruled area 3 mm. square. The 9 primary 1-mm. squares thus formed are easily identified because adjacent ones are differently subdivided. For the purpose

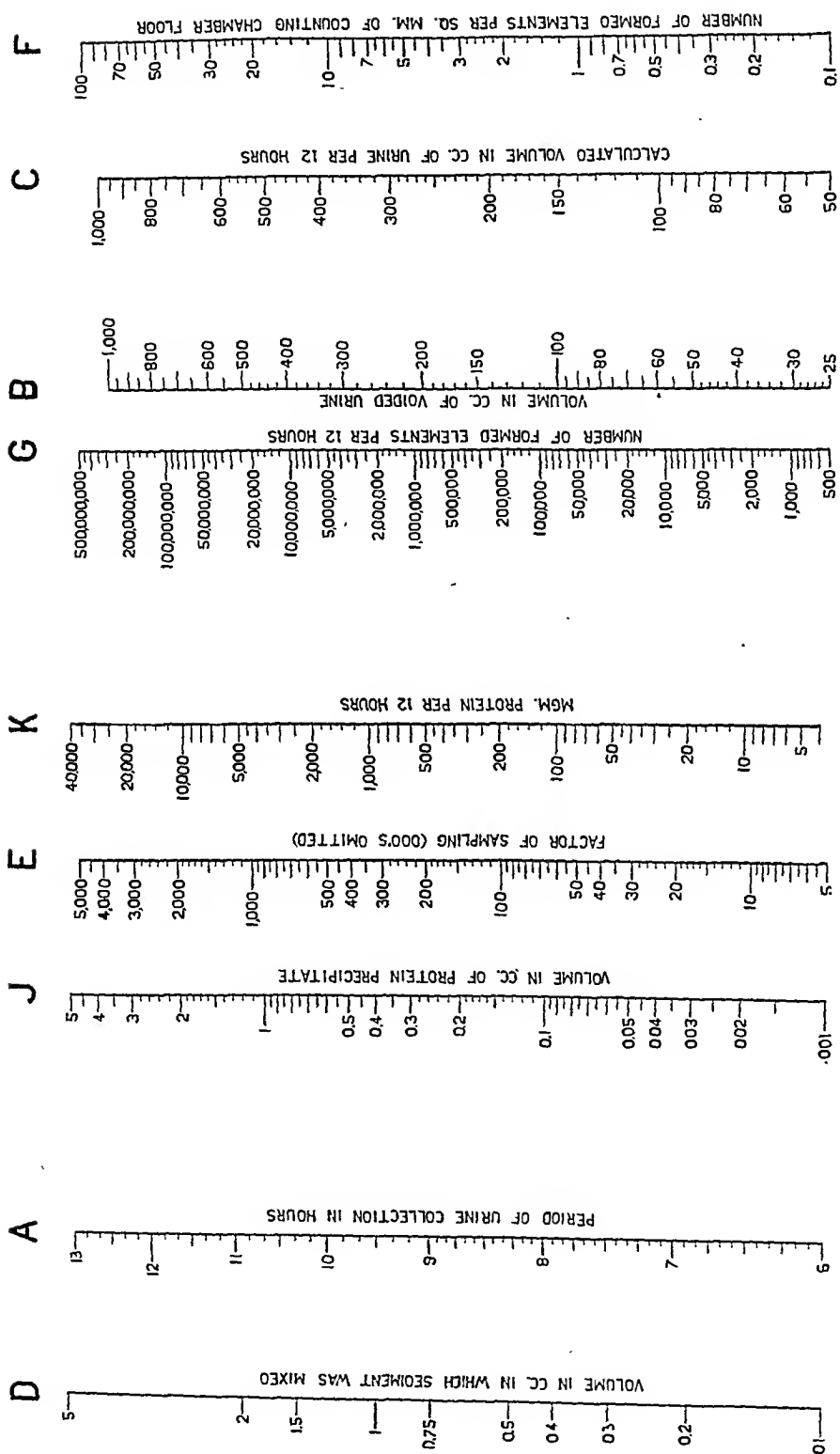
#### NOMOGRAPH FOR THE COUNT OF URINE SEDIMENT (ADDIS).

To use the nomograph place a straightedge across the two designated scales, intersecting them at given values and read at the intersection with a third scale a derived value. The scales A, B, D, F and J include the original data obtained in the study of the urine. The scales C, E, G and K give derived data. To calculate the count of the urine sediment:

1. Using scales A and B, obtain a value on scale C.
2. Using the newly found point on scale C in connection with scale J, read from scale K. (Scale K applies to Dr. Addis' modified technique for protein, using a 6.5-cc. graduate centrifuge tube. For the original technique using a 13-ml. tube, divide the obtained value by 2.)
3. Using scales C and D, read from scale E.
4. Connecting the obtained point on scale E with successive points on scale F, read from scale G the values for the respective formed elements.

$$\text{Formulae for checking: } C = \frac{12 B}{A}. \quad G = 1000 \text{ CDF}. \quad K = 7.2 \text{ CJ}.$$

\* Nomographic charts  $8\frac{1}{2}$  by 11 inches in size may be obtained from J. W. Stacey, Inc., Flood Building, San Francisco, Calif., at a cost of twenty-five cents each.



of computation with the nomograph, the 1-mm. square is taken as unit area in terms of which the elements are enumerated.

As with all procedures in which a distribution within a large quantity is estimated by enumeration in small samples, the count of the formed elements of the urine is subject to an unavoidable error due to chance variations of distribution in the samples counted. Such an error may be considerable, and it is of value to know its size.

One index to the magnitude of the error of sampling in the sediment count of the urine may be obtained from Scale E, which gives the number of thousands of formed elements per 12 hours represented by 1 element per sq. mm. of counting chamber floor. For example, if the point obtained on Scale E should be 40, each cast or cell in an average sq. mm. of counting chamber floor would represent 40,000 in the 12-hour urine, an error of 1 cast or cell per sq. mm. would cause an error of 40,000 in the total count, an error of 10 per sq. mm. would make a difference of 400,000 in the total, and so forth.

The factor of size of sample demands particular consideration in the cast count, where the upper limit of normal is only 5000 to 10,000. Here, for instance, with a reading of 40 on Scale E, it would be meaningless to glance over 1 sq. mm., find 1 cast, and conclude that there were 40,000 casts in the 12-hour excretion. Enough squares must be counted so that an error of a few elements in the number counted makes a difference which falls well within the limit of normal. It is consequently suggested that the "factor of sampling," as Scale E has been labeled, be calculated before the actual count is made, so that one can have in mind the significance of a single cell or cast.

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## PNEUMOCOCCUS ANTIBODY SOLUTION IN THE TREATMENT OF LOBAR PNEUMONIA.

### RESULTS IN 130 CASES.

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THE specific treatment of the pneumococcic pneumonias has received considerable attention in recent years. For a time interest was centered more or less on *Pneumococcus* Antibody Solution

(Huntton's Antibodies), but more recently attention has been confined to the use of serum almost to the exclusion of the other product. We believe that this is, to some extent, unfortunate. The antibody solution has been shown in the careful studies of Conner<sup>1</sup> to reduce the mortality in all types of pneumococcic pneumonia from 30 to 11 per cent approximately, and in the studies of Cecil and Larsen<sup>2</sup> from 28 to 21 per cent. In Type I cases the reduction was from 22 to 13 per cent, and in Type II from 40 to 28 per cent.<sup>2</sup> In cases of Type I pneumonia treated within 48 hours of onset, deaths decreased from 23 to 9 per cent.<sup>3</sup> This compares favorably with results obtained with Felton's serum in Type I and Type II cases. Conner's work shows antibody solution to be of value in Type III and Group IV pneumonias, in which serum is ineffective, while Cecil's does not.

Although antibody solution is occasionally productive of chills and a rise in temperature when injected intravenously, we did not encounter the numerous and severe reactions described by Conner and Cecil, and believe this preparation decidedly less objectionable than serum on this score. We are informed that the pyrogenic property of the earlier preparation of antibody solution, which was used by Cecil and Conner, was largely eliminated by a change in the distilled water used in its manufacture, and our experience bears this out.

This study comprises 130 treated and 52 untreated cases observed from 1927 to 1931 inclusive. No effort was made to form a control group, but the untreated cases serve roughly as controls. These represent, for the most part, cases in the care of physicians who were not interested in Pneumococcus Antibody Solution. These patients received no other specific treatment. Oxygen was used in a few, and a few were given blood transfusions, but for the most part their treatment consisted of careful nursing and dieting, with administration of circulatory stimulants when necessary. The solution was not reserved for selected or favorable cases, but rather the contrary, so that the treatment group includes a fair proportion of "bad risks." Treatment was given, if at all, without regard to age of patient, complications, or day of illness. Although every effort was made to have complete bacteriological studies on every case, and to give treatment early and adequately, a considerable proportion of cases escaped some part of the routine. We believe, however, that this performance is as good as can be obtained in an open hospital and in private practice, and perhaps has an added value as demonstrating what results may be expected under these, that is, under ordinary conditions.

Typing was done by the Avery method, the results from the peritoneal exudate of the mice being checked by heart blood cultures. In addition, direct plates of sputa were made in order to detect more surely the non-pneumococcic cases.



**Treatment.** Specific treatment was started as soon as the clinical diagnosis was made, and before the completion of bacteriologic studies, because of the well recognized importance of beginning injections of either antibodies or serum as early in the disease as possible. If the infection proved not pneumococcic, treatment was discontinued. Although expensive, this step saved valuable time in many cases. In more than half the cases early diagnosis was greatly aided by the Roentgen ray, and we are indebted to Dr. George U. Pillmore for his coöperation in this feature. The dose of antibody solution was usually 50 cc. intravenously 3 to 4 times a day in adults and 25 cc. in children. When the intravenous route was not feasible, intramuscular injections up to 50 cc. per dose were used. After a little experience with the solution, fear of reactions was lost and doses were enlarged in some instances to 100 cc. t. i. d. in adults and 50 cc. in children. The average total amount of antibody solution used was 460 cc. for the perfectly controlled group and 343 cc. for the imperfectly controlled group of adults, and 193 cc. for children. The largest amounts given were 1200 cc. intravenously to a man aged 37 years over a period of 13 days, and 650 cc. intramuscularly to a child aged 1 year over a period of 7 days. In neither was there any reaction and both recovered.

TABLE 1.—RESULTS OBTAINED WITH PNEUMOCOCCUS ANTIBODY SOLUTION IN LOBAR PNEUMONIA IN SUBJECTS 12 YEARS AND OVER.

	Lived B.C.	Died B.C.	Mortality, per cent.	Average days ill.
<i>Perfectly Controlled:</i>				
Type I . .	3 0	2 1	40	
Type II . .	3 1	3 1	50	
Type III . .	8 4	1 0	11	
Group IV . .	18 1	2 1	10	
	<hr/> 32 6	<hr/> 8 3	<hr/> 20	24.2
<i>Imperfectly Controlled:</i>				
Type I . .	2 0	4 4	66	
Type II . .	1 0	1 1	50	
Type III . .	5 0	3 0	37	
Group IV . .	9 0	3 2	25	
Untyped . .	11 0	0 0	0	
	<hr/> 28 0	<hr/> 11 7	<hr/> 28	25.3
<i>Untreated:</i>				
Type I . .	4 0	3 2	43	
Type II . .	4 0	0 0	0	
Type III . .	2 0	3 2	60	
Group IV . .	4 0	2 2	33	
Untyped . .	7 0	4 0	36	
	<hr/> 21 0	<hr/> 12 6	<hr/> 36	25.6

Perfectly controlled: Treatment begun within 72 hours of onset, adequate dosage.

Imperfectly controlled: Treatment started late, inadequate dosage, etc.

B.C.—Blood culture positive.

Average days ill: The duration of the disease from onset to discharge from hospital of uncomplicated recovered cases only.

A distinct impression was obtained that the larger doses were more effective, especially in producing early crises. The large doses too, were possibly more economical than the small, as the total of solution used was less when the illness was quickly terminated. Treatment was continued for 24 hours after the temperature first reached normal, either in full, or in half doses, as in several of the early cases the temperature again rose to its former height when injections were discontinued immediately after the crisis, or lysis.

TABLE 2.—RESULTS OBTAINED WITH PNEUMOCOCCUS ANTIBODY SOLUTION IN LOBAR PNEUMONIA IN SUBJECTS UNDER 12 YEARS.

	Lived.	Died.	Mortality, per cent.	Average days ill.
Treated. . . .	48	3	6	19.8
Untreated . . .	12	7	37	24.1

Very few children studied bacteriologically. Antibodies given mostly intramuscularly.

**Comment.** It is realized that the numbers included in each group are too small to be of great statistical value. However, the total mortality for the various groups seems significant. Thus the mortality of untreated adults is nearly twice that of the adequately treated group, the imperfectly treated group falling between. Of more significance are the results in those cases with positive blood cultures. Of 13 cases with positive blood cultures in the untreated and the inadequately treated groups all died, while of 9 such cases in the well treated group 6 recovered. An observation not to be reduced to statistics, but very impressive to the clinician, was the rapid conversion of not a few highly toxic cases with rapid pulse, cyanosis and delirium to a much more favorable state, even though an early crisis did not result. One gained the impression that the solution was life saving in such instances.

The average duration of the infection in the treated and untreated cases differed little in the adults, although more materially in children. It might be inferred that the effect of the antibody solution was to combat the more severe toxic manifestations of pneumonia and possibly to sterilize the blood stream, thus reducing mortality, without shortening the course of the infection.

Antibodies appeared to have a distinctly favorable effect in Type III and Group IV cases in our series, which is in accord with the reports of Conner and of Huntoon.<sup>5</sup> This is an observation of definite importance. In the group of children the mortality of the untreated is much greater than the average for lobar pneumonia, and this gives an exaggerated importance to the effect of antibody solution. On the other hand, we feel that the solution was of considerable benefit in this group. Of importance is the fact that such results as were obtained were secured by means of intramuscular administration for the most part. In this connection the results of Cecil and Baldwin<sup>4</sup> with subcutaneous injections are of interest. These, although inferior to those following the intravenous route, were worth while, the mortality reduction being from 39 to 24 per

cent in cases treated within 48 hours of onset of the infection. It might reasonably be supposed that intramuscular administration would be more effective than subcutaneous, and it is our belief that antibody solution given into the muscles of children, when intravenous administration is not feasible, is not only distinctly worth while, but greatly enlarges the field of usefulness of the method.

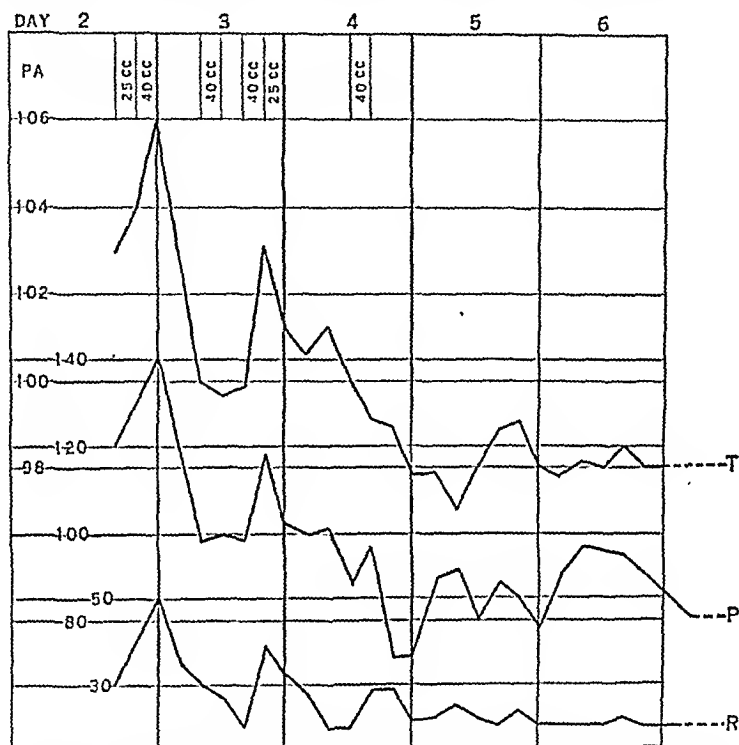


CHART 1.—T. C., age 9 years. Intravenous injections of pneumococcus antibody solution continued in spite of an initial rise of temperature. Early crisis.

We feel that cases of lobar pneumonia, which for one reason or another cannot be diagnosed bacteriologically, should, nevertheless be treated specifically, as the great majority of such pneumonias are due to pneumococci, 83 per cent according to Cecil and Larsen. For this purpose Pneumococcus Antibody Solution is logically the method of choice, since it is effective against Types I, II and III, and Group IV pneumococci, while the use of serum is confined to Types I and II. On the other hand, we by no means advocate the indiscriminate use of antibodies. Whenever at all possible the bacteriology of sputum and blood should be determined, and the remedy discontinued in non-pneumococcic cases, in which the injections are useless, expensive, and harmfully annoying to the patient.

*Complications.* Empyema occurred once in the well managed cases, 4 times in all others. Delayed resolution was observed twice in those inadequately treated. Otitis media and mastoiditis accompanied the pneumonia in several of the children.

*Reactions.* A fear of dangerous reactions has remained fixed in the mind of many physicians after the experiences of Conner and of Cecil with Pneumococcus Antibody Solution as originally manufactured. In our series of cases harmful reactions did not once occur. In 2 adults a chill with a rise of fever to  $106^{\circ}$  occurred after the administration of 100 cc. of solution intravenously, and in 1 adult after a dose of 50 cc. In a 4th adult a mild but similar reaction followed a dose of 90 cc. A dose of 25 cc. in a child aged 10 years caused a similar chill and rise of fever to  $106^{\circ}$ . The pulse and respiration were not much affected, nor were there any other manifestations. The reactions come on from 2 to 4 hours after the injections. In each case the reaction was followed promptly by a pseudocrisis with improvement in the general condition of the subject. Other manifestations were recorded as reactions, such as increase in rate of respiration, nausea, pain in the back, but careful review of the records make it questionable whether these can be attributed to the solution. Thus, an incidence of five definite reactions, none harmful, in several hundred injections, does not furnish reason to fear this result. In all these cases similar doses were given either before or after the reactions without any untoward effect. No systemic reactions followed intramuscular administration, and local reactions were remarkably mild even when large quantities were injected.

Pneumococcus Antibody Solution was made available for ward patients of Bryn Mawr Hospital through the generosity of the late Mr. Samuel Rea and other members of the Board of Trustees, the late Mrs. Samuel G. Dixon and others of the Women's Board of Managers, and others.

**Summary.** Pneumococcus Antibody Solution was observed to effect a definite reduction in mortality in 130 cases of lobar pneumonia of all types and ages as compared with 52 cases not specifically treated.

It appeared to be of distinct value in Type III and Group IV cases, as well as in Types I and II.

It appeared to be of value when given intramuscularly in infants and children.

Its effect was most marked in cases treated within 72 hours of the onset of the infection, and with large doses.

It is rarely productive of reactions.

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2. Cecil, R. L., and Larsen, N. P.: Clinical and Bacteriologic Study of 1000 Cases of Lobar Pneumonia, *J. Am. Med. Assn.*, 79, 343, 1922.
3. Cecil, R. L., and Plummer, N.: Pneumococcus Type I Pneumonia, *Ibid.*, 95, 1547, 1930.
4. Cecil, R. L., and Baldwin, H. S.: Treatment of Lobar Pneumonia with Subcutaneous Injections of Pneumococcus Antibody Solution, *J. Pharm. and Exp. Therap.*, 24, 1, 1924.
5. Huntoon, F. M.: Personal communication.

## BOOK REVIEWS AND NOTICES.

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LABORATORY MEDICINE. By DANIEL NICHOLSON, M.D., Member of the Royal College of Physicians, London; Assistant Professor of Pathology, University of Manitoba, etc. Pp. 566; 124 illustrations, 3 colored plates. Second edition, thoroughly revised. Philadelphia: Lea & Febiger; 1934. Price, \$6.50.

THIS is a compact but comprehensive work dealing with the modern phases of laboratory medicine—amply illustrated and written in simple, easily followed style. The chief advantage of this book over other modern works lies in the author's unique method of organization and presentation of the large amount of material, both old and new, that has accumulated in clinical pathology. The selection of methods is based primarily on simplicity, with simple directions in technical details and lucid interpretations. For both students and technicians the sources of error, with simple reasons, follow each procedure. The general practitioner will find the common routine procedures briefly and conspicuously outlined. These are procedures that can be done in office and bedside practice and because of their simplicity they enable the practitioner to use and enjoy the rapidly expanding knowledge in laboratory medicine. A few of these procedures are modern skin tests with illustrated reactions, prophylactic laboratory treatment of measles, whooping cough, etc., accompanied by suitable simple laboratory tests. The colored plate illustrating Benedict's urinary sugar reactions, to the Reviewer, is unique and satisfying.

For everyone's use the indications for expensive tests and rare or unusual examinations are given, which, if followed, will prevent considerable duplication of results with saving of time and expense. The procedures are first given in brief in heavy type, followed in detail in ordinary legend form. This thoughtfulness on the part of the author will prove a time saving to many. An inspection of the book should convince one of its value.

J. B.

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FORMES, VIE ET PENSÉE. By J. BEAUVERIE and others. Pp. 419; illustrated. Lyon: Librairie Lavandier, n.d. Price, 20 fr.

THIS, the fourth of the series published by the Lyons group on philosophic and biologic aspects of medicine, deals with structural relation between crystalline and organic forms, elementary and embryonic structures, the relation of structure to adaptation, endocrine influences and a final synthesizing chapter on form and function. It supplements the preceding volume on "Les Rythmes de la Vie" (reviewed AM. J. MED. SCI., 186, 581, 1933). The same method has been followed, as previously, of having a different member of the group write each chapter—thus providing a breadth of points of view even if at the cost of some overlapping and differences of opinion. The Abbe Monchanin, who, as in the past, contributes the final chapter, invokes the rhythms of life and mind as incitants to a return toward God and his works. Though little or no proof is attempted or possible, the book will prove stimulating along little traveled lines of thought.

E. K.

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HUMAN SEX ANATOMY. By ROBERT LATOU DICKINSON, M.D., F.A.C.S. Pp. 145; more than 1000 illustrations. Baltimore: The Williams & Wilkins Company, 1933. Price, \$10.00.

THE previous publications of the National Committee on Maternal Health have covered various aspects of sex and the sex relation. As a

definite program developed, the need for an atlas, a basic portrayal of the normal anatomy of the two sexes and of the anatomy of coitus and contraception became apparent. To meet this demand Dr. Dickinson has edited the present volume on Human Sex Anatomy.

The book is divided into two parts, the first section (132 pages) correlates the atlas proper with a description of the plates, their source and the scales upon which they were drawn, with a running commentary upon the normal and abnormal anatomy of the genital organs, as well as the anatomical and functional relations exercised in coitus. Frank as the discussion and illustrations are, one is not a little surprised to find that one plate, not included in the atlas, is to be sent to medical purchasers of the book only at their personal request.

The atlas comprises 172 figures, but there are over a thousand separate drawings on these plates. Dr. Dickinson's pencil has been as able as his pen was fluent and the many original drawings reflect not only his ability as an artist of consummate skill but his thorough understanding, as a physician, of the point he wished to illustrate.

The anatomy of the female reproductive organs in diagram, line sketch and half tone from hundreds of sources show every possible view by dissection and sagittal and oblique section, illustrating the part these organs play in the sex act. The anatomy of the male genital structures is portrayed in an equally exhaustive manner. The anatomy of coitus represents an entirely new approach to an understanding of the anatomical relations involved in this dual function in the different positions portrayed. The anatomy of contraception illustrates many methods of contraception and many devices which are used.

This book certainly fulfills the need as stated. To those whose advice is sought regarding sex, sexual or marital problems, the text will offer much. Many problems in sex research are suggested. P. W.

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COLD SPRING HARBOR SYMPOSIA ON QUANTITATIVE BIOLOGY. Volume 1. Pp. 239; illustrated. Cold Spring Harbor, L. I., N. Y.: The Biological Laboratory, 1933. Price, \$2.90.

IN furtherance of this Laboratory's purpose of developing the field of quantitative biology through the coöperative effort of biologists, chemists, physicists and mathematicians, a distinguished group was invited there last summer to carry on their investigations, and during one month to give lectures and take part in symposia. This monograph, presenting 28 topics, extending over a wide range, represents the first fruits of an interesting and important experiment in the acquisition and diffusion of scientific knowledge. The method has already so demonstrated its value that fortunately we may expect a series of volumes which will make available these "last words" to a wide circle. For they represent a galaxy of stars that it would be hard indeed to surpass. Lectures (revised and grouped for publication) by Hans Müller and Abramson on electrophoresis, the diffuse double layer, the stability of colloids, and so on, unite with studies on conductance by Cole, on agglutination and phagocytosis by Mudd, on the biophysics of respiratory proteins by Svedberg. Neurophysiology is represented by Cole, Gasser and A. V. Hill, osmosis by Briggs, Osterhout and Ponder, oxidation-reduction by Barnett Cohen, Chambers and Michaelis. Only one article on pH appears (by D. A. MacInnes), while some aspects of the physical chemistry of the blood are presented by van Slyke, and the electric impedance of cell suspensions is given by Hugo Fricke, the first director of the biophysical laboratory (1928). Short discussions of various lectures add to the background. If this initial high standard is maintained, it is difficult to see how a worker in this field can do without these volumes or fail to attend future symposia at Cold Spring Harbor. E. K.

## NEW BOOKS.

*External Diseases of the Eye.* By DONALD T. ATKINSON, M.D., Consulting Ophthalmologist to the Santa Rosa Infirmary and the Nix Hospital, San Antonio, Texas, etc. Pp. 704; 479 illustrations. Philadelphia: Lea & Febiger, 1934. Price, \$7.50.

*Chinese Medicine.* By WILLIAM B. MORSE, M.D., LL.D., F.A.C.S. Vol. XI of Clio Medica series. Pp. 185; 20 illustrations. New York: Paul B. Hoeber, Inc., 1934. Price, \$2.50.

*The Medical Clinics of North America, Vol. 17, No. 5 (New York Number—March, 1934).* Pp. 324; 32 illustrations. Philadelphia: W. B. Saunders Company, 1934.

*Medicine. A Voyage of Discovery.* By JOSEF LÖBEL, M.D. Translated from the German by L. MARIE SIEVEKING and IAN F. D. MORROW. Pp. 334. New York: Farrar & Rinehart, Inc., 1934. Price, \$3.00.

*The Cyclopedia of Medicine, Volume 8.* GEORGE MORRIS PIERSOL, B.S., M.D., Editor-in-Chief, and EDWARD L. BORTZ, A.B., M.D., Assistant Editor. Chief Associated Editors: W. WAYNE BABCOCK, A.M., M.D., CONRAD BERENS, M.D., P. BROOKE BLAND, M.D., FRANCIS L. LEDERER, B.S., M.D., A. GRAEME MITCHELL, M.D. Pp. 1083; illustrated with half-tone and line engravings, also full-page color plates. Philadelphia: F. A. Davis Company, 1933.

*Japanese Medicine.* By Y. FUJIKAWA, M.D. Translated by JOHN RUHRAR, M.D., Vol. XII of Clio Medica series. Pp. 114; 8 illustrations. New York: Paul B. Hoeber, Inc., 1934. Price, \$1.50.

*Brucella Infections in Animals and Man.* By I. FOREST HUDDLESON, Department of Bacteriology and Hygiene, Michigan State College. Introduction by WARD GILTNER, Dean, Division of Veterinary Medicine, Michigan State College. Pp. 108; 24 illustrations, 2 in colors. New York: The Commonwealth Fund, 1934. (Price not given.)

*A Short History of Some Common Diseases.* By DIVERS AUTHORS. Edited by W. R. BETT, M.R.C.S. (ENG.), L.R.C.P. (LOND.), late Resident Medical Officer, Princess Elizabeth of York Hospital for Children, Shadwell, Eng., etc. Pp. 211. London: Oxford University Press, 1934. (Price not given.)

*Coccidia and Coccidiosis of Domesticated, Game and Laboratory Animals and of Man.* Monograph No. 2, Division of Industrial Science, Iowa State College. By ELERY R. BECKER, D.Sc., Associate Professor of Protozoology, Iowa State College. Pp. 147; 25 illustrations. Ames, Iowa: Collegiate Press, Inc., 1934. Price, \$2.50.

*The Surgical Clinics of North America, Volume 14, No. 2 (New York Number—April, 1934).* Pp. 293; 71 illustrations. Philadelphia: W. B. Saunders Company, 1934.

*Acute Intestinal Obstruction.* By MONROE A. McIVER, M.D., Surgeon-in-Chief, Mary Imogene Bassett Hospital, Cooperstown, N. Y. Pp. 430; 62 illustrations. New York: Paul B. Hoeber, Inc., 1934. Price, \$7.50.

## NEW EDITIONS.

*Essentials of Medical Electricity.* By ELKIN P. CUMBERBATCH, M.A., B.M. (OXON.), D.M.R.E. (CAMB.), M.R.C.P., Medical Officer in Charge, Electrical Department, and Lecturer on Medical Electricity, St. Bartholomew's Hospital, etc. Pp. 508; 132 illustrations and 15 plates. Seventh edition, revised and enlarged. London: Henry Kimpton, 1933. Price, 10/6.

# PROGRESS OF MEDICAL SCIENCE

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## NEUROLOGY AND PSYCHIATRY

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UNDER THE CHARGE OF

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## THE PRACTICAL SIGNIFICANCE OF PSYCHOTHERAPY IN GENERAL PRACTICE.

WE pride ourselves on the scientific progress of medicine but all the while we may be blinding true sight by a gaudy delusion. Instruments of precision have enhanced our diagnostic ability; microscope and test tube have reduced symptoms to perceptible causes and effects. We jostle molecules and bacteria about as we might trained fleas, we reduce complaints to pathologic changes, and our findings make for us a "case," the clinical course and ultimate results of which we are fairly well able to predict.

The "day of specilization" has removed us still farther from our patient as he would have us see him, and some of us confine ourselves with concern over the gastro-intestinal tract while others of us are content with meting out organotherapy. Truly, a "large scale industry arises, in the running of which there is never a moment's leisure for personal contact between physician and patient and wherein there is no longer a trace of magnetic rapport between the soul of the healer and the soul of the healed."<sup>1</sup>

Because we have been too engrossed in organs and systems, because we have failed to consider the patient in his entirety, his setting in life, his biologic peculiarities, we have missed much to be interpreted as pathologic change not measurable by laboratory methods and have driven our patients to cults and sects for the understanding that we denied them.

Only recently the director of a large outpatient dispensary said: "Today I saw a man who complained of vague surging sensations here and there throughout his body. He remarked that upon dropping his arms to a dependent position at his side all these feelings disappeared. I asked him how many doctors had seen him and he rather boastfully replied 'Oh, I should say between thirty and forty.' Now this man had a blood pressure that, while not strikingly abnormal, warrants



investigating, but outside of this I could find nothing. Either he has something most unusual which all of these men have missed or he is psychoneurotic and it is our job to find out why and do something about it."

How common an example this is of that great cross-section of material seen in our dispensaries, in our offices and upon the wards of our institutions. How readily and willingly we label such a patient "psychoneurotic" and then limit our treatment to telling him it is "just a case of nerves" and send him on his way.

It is useful to recognize three types of these disorders into which the majority of such problems will fall. These are:<sup>3</sup> (a) Conversion hysteria, (b) anxiety states and (c) obsessive states.

**Hysteria.** Hysteria is the great mimic of somatic disease, particularly simulating any number of neurologic disturbances. To understand the motivation of the symptom we must scrutinize the forces leading to its production by a thorough genetic-dynamic study (*i. e.*, a chronologic study of important life factors dating from birth). With early recognition, an hysterical phenomenon may be checked at its beginning by common sense treatment, or with lack of understanding it may be encouraged in its fixation by making a diagnosis of physical disease.

Though this is not the place for a didactic discussion of hysteria, it would be well to point out the more common forms in which it finds expression.<sup>4</sup> Among them are:

1. Hysterical convulsions closely simulating the *grand mal* attacks.
2. Somatic changes on an hysterical basis, as: (a) Anesthesia to touch, pain, temperature and proprioception; (b) hyperesthesias; (c) paresthesias.
3. Another large group presents motor involvement, such as: (a) Hysterical paralyses—monoplegias, paraplegias, hemiplegias; (b) contractures—torticollis; (c) abnormal movements—astasia, abasia, chorea, trembling movements; (d) loss of voice; (e) hysterical aphasias; (f) benign respiratory tics, as sneezing, hicoughing, dyspneas; (g) spasms—esophageal globus, vomiting, vaginismus, etc.
4. Sensorial changes do not escape; we frequently encounter olfactory and gustatory perversions, loss of hearing, vertigo and visual alterations ranging from restriction of the visual fields and hemianopia to blepharospasm.

**Anxiety States.** One of the most interesting and common symptom pictures of "nerves" is that seen in attacks of dyspnea, palpitation, sweating, vertigo, precordial discomfort and often gastro-intestinal manifestations with the predominating emotional accompaniment of apprehension, a vague fear of impending danger. Earlier writers attributed these states to frustrated sex excitement or unfulfilled erotic activities. However, with the growing appreciation of a genetic-dynamic study of a problem, we have come to see the anxiety attack resulting not from misdirected sexual activity alone but from any number of daily stresses and strains.

These were the cases so frequently misdiagnosed as hyperthyroidism; these were the cases we called "post flu hearts" in 1918 and 1919 because of the seeming cardiac disorder. An important psychiatric dispensary in this country registered only 80 cases of anxiety states

in the year 1926 when this country was without economic stress, but in the year 1932, when we began to feel the pressure of the depression, 232 such cases were listed.<sup>5</sup>

As anxiety states one may encounter: 1. General irritability—a response to overexcitation, usually with marked tension, pathologic alertness and hyperactivity of auditory sense, particularly.

2. Anxiety attacks in which the outstanding feature is fear—fear of death, fear of a stroke, fear of insanity—together with which there is a disturbance of one of the levels of physiologic functioning, as:

(a) Cardiac with palpitation, precordial distress, tightness, fainting, smothering, sinking spells, pain around the heart and substernal pressure.

(b) Respiratory—dyspnea, shortness of breath, pain in the chest, tightness in the throat.

(c) Gastro-intestinal—diarrhea, constipation, nausea, vomiting, and belching; with the possibility of others, as (d) frequency in micturition, vertigo, giddiness, tremor and trembling, night terrors and parasthesias. Of such common occurrence are these and strikingly like organic conditions that they have frequently been diagnosed “angina pectoris, pseudoangina, heart murmur, soldier’s heart, effort syndrome, spastic colon, appendicitis, cecal stasis, gastropathy and gastric ulcer.”

**Obsessional States.** This third and last group, though interesting, is less frequently encountered, and because of the involved psychopathologic factors of this group treatment of these patients should not be undertaken by the general practitioner.

It is diagnostic of an obsession that the patient knows its unreality and feels it is derived from something apart from his self. He is conscious of the absurdity involved in his thinking and may attempt to resist its recurrence.

The disorders of obsessive character are doubts, fear states, thoughts and acts.

We are all familiar with the doubt of having turned off the gas heater after retiring, of having put the right letter in the right envelope after posting them. This individual will say to himself, “I *know* I’ve done it but I *feel* that I haven’t.”

Similarly, these peculiarities can be analyzed and explanation may be found in the influence of unconscious processes.

**General Considerations.** A survey of the literature in the past year reveals conclusively the awakening of medical consciousness to the importance of these disorders in general practice. Gillespie’s article,<sup>6</sup> perhaps, is outstanding because of its forcefulness in stating the case. In Guy’s Hospital about three-fourths of the registered cases were psychoneuroses not resident at the hospital, while but one-fourth comprised the group of institutionalized psychoses. Pervading all practice from gynecology to dermatology are these cases, which masquerade as clinical entities.

There is the current impression that psychotherapy is a specialist’s job and necessitates special equipment. However, most of these illnesses require no special technique and can be handled by a common sense approach. The requisites for efficient psychotherapy are a “profound knowledge of human nature,” a “good knowledge of general medicine” and ability to spend sufficient time on each individual.

One cannot overemphasize the importance of a good history and clinical observation. Should the physician ask himself what knowledge of psychology he need possess, the answer will be "a knowledge of how psychologic factors can cause what looks like disease."

A most necessary part of the examination is the physical part. It assists in establishing rapport and confidence in addition to having the patient feel that due credit is being given every possibility. Should a "lesion" be found it must be considered in terms of the complaints.

Psychologic examinations are of two types: A "cross-section" examination, in which the complaints are focussed upon and the present status of the patient determined; and a longitudinal study considering the history of the patient himself as well as his illness. The former makes for diagnosis, while the latter is a most useful guide in treatment.

If, in getting the history, the physician focusses attention on the time of origin of the symptoms he will uncover the factors which have produced them. Most common of these are financial concern, domestic affairs, marital difficulties, promotion, demotion, etc.

Best results in the treatment of hysteria are obtained by persuasion. In this manner a "paralyzed" member may be restored and yet the change has been objective enough to impress the patient and, by establishing steadfast *rapport*, make further treatment possible. This method, however, cures only the symptom; but, after all, in many hysterics "cure of the symptom is nearly all that is required."

It may be seen by this survey that no special apparatus is required to produce results but perseverance, accurate investigation and willingness to spend a reasonable time soon after the patient first presents himself.

Obstacles to psychotherapy are pointed out by L. B. Hill,<sup>7</sup> who believes that the cause of the dissatisfaction with current psychotherapeutic activities is to be found in the absence of close association between psychotherapeutic thinking and psychopathologic information. Not all physicians have therapeutic talent. It is essential that they do not have a defensive attitude toward bringing to light the patient's emotional difficulties.

R. W. Hall<sup>8</sup> believes that psychotherapy can be organized in two ways: (1) By the creation of a special psychotherapeutic department to be relieved of all administrative routine; and (2) by the development of a psychotherapeutic ability in promising personnel. At St. Elizabeth's, some 15 years ago, Dr. White innovated a special psychotherapeutic department. At the present time the hospital continues with this method and has three psychotherapists, all of whom are analysts, to deal with the treatable type of cases. Psychotherapeutic problems are presented along two main lines—adaptation and insight. The development of psychotherapeutic talent in promising personnel is the most practical plan. It is not difficult to pick out those who have ability to establish *rapport* and gain confidence and respect of their patients. The service possibilities of the junior physician should not be ignored, and those who have some psychotherapeutic ability should be given more time to deal with such problems. Although only a small proportion of mental hospital patients are suitable for intensive psychotherapy, many might be helped by occasional interviews. Much importance should be attached to the initial interview after the patient

is admitted to the hospital. His first impression is usually a lasting one and every effort should be made to make this favorable. The initial interview should orient the patient as to the circumstances and reasons for his hospitalization and should outline to him in a frank and systematic way what the hospital plans to do in his case, and what is expected of him. Of no less importance is the psychotherapeutic attention given just before discharge. At this time there should be a review of the patient's assets and a consideration of his past psychiatric experiences. We cannot disregard the importance of nurses and attendants in a psychotherapeutic organization.

At Stockbridge, H. K. Richardson<sup>9</sup> states that no one school is followed in their approach; however, it is principally a genetic dynamic developmental formulation of causal relationship and factors. It attempts to develop a permanent solution, understandable to the patient. When the patient enters Stockbridge, the history is obtained from him and his relatives; he is assigned to his hospital unit or "inn," and he is put on a regulated schedule of work, play, relaxation and rest. Daily interviews are held in which historical relationships as to his family life, his reaction to parents, dreams, preoccupations, or disturbances of childhood, adolescence, and adulthood, and evidences of maladjustment of the patient are gone into. The patient learns to "talk things out," and the doctor assumes the attitude of a sympathetic listener. If there is need, suggestions may be made or word association may be used to uncover material that is otherwise hidden. Reëducation proceeds on three levels: (1) Understanding of the problem and outlining a procedure to correct them by the patient; (2) application of this technique in the friendly limited environment of the hospital; and (3) an attempt to apply this same procedure away from the hospital and without the crutches upon which the patient has leaned. The therapy is further supplemented by five pamphlets: One furthers his information on levels of integration and gets him away from the mind-body conception; a second treats the possibility of somatic response to emotional difficulties; a third discusses maladaptation; a fourth deals with nature and function of his neurosis; and the last is a treatise on rest and relaxation as it may be applied.

Concerning psychotherapy in public mental hospitals, R. H. Hutchings<sup>10</sup> feels that the removal of the patient from his home to the institution is of first importance. Thus we separate him from the difficulties of the environment in which the psychosis developed and conditions which are likely to prolong it. Hospitalization gives him an opportunity to think of his conflicts as remote and takes him into an environment in which he can begin to reconstruct his past experiences and perhaps develop new emotional attitudes. The first impression the patient receives on entry is of paramount importance. The first contact that the prospective patient makes with the institution is in the person of the transfer nurse or attendant whose appearance and greeting, poise and tact are determinants in the impression to be gained by the patient. The receiving room or building should be inviting in appearance. The personality of the physician whom the patient meets in the reception room should be attractive. All these contacts with representatives of the hospital play important rôles in the establishment of rapport. The time to establish rapport, to gain good

transference, is the time of making the formal mental examination. The importance of making this examination as soon as possible after admission and of keeping the patient practically isolated until it is done is emphasized. The value of frank talks with the physician cannot be too highly estimated. Patients who are at all communicative appreciate it and find relief in talking over their conflicts and problems. One's object is to induce the patient to alter his beliefs for himself; to argue with him is merely wasting time and may bring about a negative transference. The most important psychotherapeutic adjunct is occupational therapy. The instructor must be a good teacher and must be able to interest and stimulate the patient. Occupational therapy is designed to prepare the patient to enter into larger social activities outside of the institution; its aim is to reestablish his lost capacity to cooperate harmoniously in group activities. Occupational therapy is one of the most effective means in aiding him to regain his community cooperation and teamwork. Recreation and amusements afford another therapeutic adjunct. Group activities bring out the introverted type of patient and are essential in socializing his interests.

In our own University Clinic,<sup>11</sup> we found that, in 1933, 60 of 116 psychiatric consultations asked for by the General Hospital were psychoneuroses, a total of 51%. It is conservatively estimated that one-third of the cases seen in the outpatient departments of this same institution present functional problems.

Our approach<sup>12</sup> to these problems and methods of psychotherapy in this clinic is somewhat as follows:

Any patient who comes is requested to describe as fully as possible the complaints that bring him to the clinic. These obtained, the history of their development determined, then this material is supplemented by a physical and mental examination.

The story, as given by the patient, is as objective as possible, based upon concrete experiences. The complaints are stated fully and recorded in the very terms of the patient. These facts are supplemented by those obtained from relations, friends and your own observation. There is a sincere search for the factors at work, the development of the condition, its working and effects and the modifiability of the whole. We attempt to get away from such complaints as "fear," "nervousness" and "depressed" and substitute for them concrete situations and reactions in order to keep on a ground of objectivity. It is important to use, wherever possible, the patient's own expressions and terminology and to stay away from complicated terms unintelligible and confusing to our patient.

*Rapport* is essential to good psychotherapy, but it must be a healthy, normal relationship and not one of supernormal type of suggestion and of so-called transference. It should be devoid of a relationship of anticipation, devotion and excessive personal dependence. It is much more acceptable to make it a rapport between physician and problem than physician and patient. It strives to have the patient use his resources whether the doctor is there or not.

It is necessary to attack the individual problems on an open talking basis with a goal of desensitization on the part of the patient to his difficulties. Repeated "rehashing" occurs until we feel that our client now discusses his problem without the emotional turmoil that brought

him to us. There must be, however, more than aëration and desensitization; there must be concrete and personal reëxperiencing of situations with a sensing of available opportunities for readjustments.

Part of each interview is given over to an account of the last 24 hours. Past experiences are reviewed to overcome disturbing sensitiveness and other obstacles. We talk in terms of life as it occurred and occurs and not in terms of word pictures of a fixed brand of theory. The case is formulated to the patient in terms he can handle, but first he is encouraged to size up the situation himself; this is more acceptable and lasting.

Another measure used is appeal through the more personal type of rapport; a third, persuasion; fourth, an intellectual-emotional winning over to an interest and participation in the day's routine and plan; the last, and most hoped for, the building up of a philosophy of understanding and of work and rest out of the patient's *own* associative material.

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F. G. E.

#### OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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#### CONCERNING SOME RECENT CONTRIBUTIONS TO THE PHYSIOLOGY AND PHARMACOLOGY OF RHINOLOGY.

DURING the past year or so, oto-rhino-laryngology's kaleidoscope has been revolving with such bewildering rapidity that accurately to pick the prevailing pattern would require a master hand. Even so, it is clear that oto-rhino-laryngology's active phases have been chiefly in the domain of the experimental physiologist and pharmacologist, the allied branches of experimental biochemistry, biophysics and pharmacodynamics and applied experimental chemotherapeutics.

Accordingly, for the purposes of this review, have been chosen several recent contributions of seemingly basic significance and practical value not so much for their demonstration of fact as for their demonstration of method.

Under the title "Ventilation of the Nose and Accessory Sinuses: Oscillographic Method of Investigation," O'Malley<sup>1</sup> presents a preliminary communication concerning the physical and physiologic phenomena of air currents which occur in the nasal passages during the act of respiration. As olfaction in man has become of less importance, the respiratory rôle of the nose becomes the dominant function. The chief physical factors concerned in the ventilation movements of gases in Nature, and which appear to be present to some degree in the nose and sinuses, are listed as: (1) Perflation [expiration]; (2) aspiration [inspiratory]; (3) diffusion; (4) conduction; (5) radiation; (6) convection; (7) evaporation; and (8) expansion. In its present form, the oscillograph is registered on a revolving drum by a writing style attached to a tambour into whose air chamber a rubber tube, connected with the intranasal cannula conducts the air currents. For intrasinus determinations, the cannula is inserted after "proof puncture of the antrum or other accessible sinus." The mode of procedure consists of a complete detailed history and elicitation of the physical findings of the patient; transillumination, Roentgen ray and "proof puncture" of the sinuses, all of which is followed by oscillographic tracings before and after (depending on the results of) light, air and suction tests. These are described in the text and numerous oscillographic tracings, taken under numerous conditions, are presented. The author, from his observations, believes: (1) That the air in the accessory sinuses with patent ostia is in constant respiratory phase with that of the nose; (2) that their air pressure variations synchronize; (3) that air pressure variations can be shown in all parts of the nasal passages under all conditions of respiration; (4) that partial vacuum pressure in the sinuses can be demonstrated where no sinusitis exists; (5) that the same can be shown in acute and chronic sinusitis; and (6) that an influence of this mechanism in aggravating the inflammatory changes in both types of cases is indicated. Finally, the author promises to present further data on 20 other points, which he enumerates, the last of which is the "interdependence of ciliary action and air pressure variation currents."

In a comparative anatomic study, Eckert-Möbius<sup>2</sup> states that there are 3 main theories regarding the functions of the paranasal sinuses: (1) To lessen the weight of the skull and to provide certain adjustments needed in the facial skeleton, such as spacing of teeth, etc.; (2) to increase olfactory acuity, especially by sniffing; and (3) to warm and moisten the inspired air. Of these, the author recognizes only the third as being important. He considers the following evidence: (1) The accessory nasal sinuses which, beginning as outgrowths of the mucosa of the upper respiratory tract, like the nose, are lined by columnar ciliated epithelium containing goblet cells; (2) in the large and fleet mammals with an active respiratory apparatus (elephant, giraffe, buffalo), the paranasal sinuses are well developed, whereas slower moving animals, particularly those living in a watery environment (hippopotamus, walrus) whose inspired air does not need moisten-

ing, have no, or only rudimentary, sinuses; and (3) the highly pneumatized skull of the land-loving brown bear is contrasted with the virtually non-sinus-containing skull of the aquatic polar bear.

While in experiments the use of ciliated epithelium from amphibians and other lower forms may often be expedient and sometimes unavoidable, Proetz<sup>3</sup> points out that deductions made from the results obtained may not properly be applied to human membranes. Recalling that air-breathing animals are required to supply their own fluids to keep the nasal cilia beating, while the water inhabitants are not, the author insists upon the use of mammalian membranes for experimental purposes. Accordingly, and so as to approach normal conditions as nearly as possible, parallel studies of extirpated human nasal mucosa and the nasal mucosæ of rabbits *in situ* were made, both under direct vertical vision with a magnification of 104 diameters and a motion picture record to permit repeated examination and deliberate analysis. The methods and apparatus employed in these ingenious experiments—designed primarily to determine those conditions which permit, pervert or destroy the maximum efficiency of the ciliary function—are fully described and illustrated. With one exception, 22 specimens removed at operation from diseased human sinuses showed the cilia to be quite normal in appearance. The time required for a single cycle of motion in both rabbit and man varied from  $\frac{1}{4}$  to  $\frac{1}{10}$  sec. The direction of wave propagation is, or can be, in the opposite direction to that of the effective ciliary stroke. From the clinical standpoint, the most important observation is the effect of drying, which caused a cessation of ciliary activity. If allowed to continue for 15 to 18 min. the ciliary motility could not be restored by moistening. Although the results on the *in vitro* human experiments and the *in vivo* rabbit investigations presented no gross differences, "it is not intended even to suggest that they (*i. e.*, differences) do not exist until a very large amount of material shall have been seen, and until the errors possible to the rabbit experiment have been reduced as far as humanly possible."

In a "Comparison of Ciliary Activity Under *in Vitro* and *in Vivo* Conditions," Lucas,<sup>4</sup> having previously emphasized<sup>5</sup> the need for methods permitting direct observation of ciliary activity, describes such a method whereby cilia arranged in a field, as they are in the pharynx of the frog and the nasal cavity and sinuses of higher animals, may be kept under direct observation. Virtually the same ciliary responses were obtained *in vivo* and *in vitro*. Minor differences between ciliary behavior and mucous flow *in vivo* and *in vitro* may be attributed perhaps to the absence of blood circulation in the latter condition. Lucas' results have demonstrated that the cilia of the frog's pharynx in the absence of extraneous factors maintain an inactive quiescent state, and that with mechanical stimulation from any source the cilia are stimulated to activity which ceases when the cause is removed. Therefore, he says, the base line for physiologic studies of ciliary behavior *in vivo* and even *in vitro* is zero for the frog's pharynx.

In a later contribution, Lucas<sup>6</sup> gives minutiae of his method for direct observation of cilia *in situ* and illustrates his apparatus. From the evidence thus far available in the experiments on invertebrates, amphibians and mammals, he presents the following opinions: Ciliated cells do not immediately adjust themselves to new conditions



imposed by injuries to adjacent epithelium; after reversal and reimplantation of ciliated tissue in the same site, the original polarity of implanted and contiguous tissue is maintained; regenerated ciliated epithelium will have the same polarity as it originally held in relation to the tissue from which it originated if the internal and external factors are unchanged.

Quite recently, Lucas and Douglas<sup>7</sup> employed the same method along with the well-known methods of applying carbon particles to the mucous surfaces of the noses of various kinds of mammals, in order to learn the significance of the direction of mucous flow in various regions of the nose and its possible relation to physiologic and anatomic factors. In all the animals used—mouse, rat, rabbit, opossum, cat, sheep and cow—the direction of the mucous flow was toward the anterior nares, and the region of greatest ciliary activity was in the upper part of the nose, all of which is exactly opposite to the condition found in man and monkey. Furthermore, it was learned that the direction of air currents for cats was equally different from those marked out for man. Therefore, it was concluded that the direction of air currents through the mammalian nose is a factor in the development of the pattern of mucous flow and that the two are inversely correlated.

Several noteworthy contributions concerning the immediate direct effect of the various drugs used daily in the nose on the speed and continuation of ciliary activity have appeared recently.

Badertscher<sup>8</sup> used microscopic observation of the duration of the ciliary motion of the frog's pharyngeal epithelium as an indication of progressive injury to mucous membranes. The ciliary motion of infusorial cells (paramecia) was studied for comparison. It was found that the preparations employed were "rather markedly toxic." With the exception of methylene blue, the paramecia were more susceptible than the pharyngeal epithelium, the ratio being from 2 to 8 for phenol, meroxyl and eosin; from 16 to 40 for aeriflavin, pyridium, mercurochrome and gentian violet; 375 to 500 for hexylresorcinol and iodine; and infinite for quinine.

In an attempt to determine why such beneficial results follow the local applications of silver nitrate in vasomotor rhinitis, Lillic and Childrey<sup>9</sup> performed a series of experiments on rabbits, 20% solution of silver nitrate being applied to the nasal mucosa. At varying intervals afterward, the animals were killed, and sections of the nasal mucous membrane, which had been treated, were studied histologically. Following this procedure, the epithelium begins to regenerate as early as 1 week after treatment, and cilia may appear 3 months afterward. This epithelium does not appear normal, but is pseudostratified and contains an abnormal number of goblet cells. The underlying tissue is fibrous and thick, and, although it contains glands which have apparently regenerated, it is abnormal in appearance and markedly infiltrated with cells. Perhaps of greater importance in the study of vasomotor rhinitis is the fact that the nerve fibers show cellular infiltration and vacuolization. These changes in the nerve fibers may explain the beneficial results obtained in the treatment of vasomotor rhinitis by the topical application of silver nitrate solution to the membranes in the region of the nasal ganglion.

Lierle and Moore<sup>10</sup> studied the effects of various drugs on the activity of the unprotected cilia of the upper respiratory tract of man, the dog and the guinea pig: (1) A small series of determinations was made of the effects of certain drugs on the ciliary activity of strips of tissue mounted in a special microscope chamber; (2) 20 determinations were made of the effects of a larger number of drugs on the ciliary activity of the unbroken mucosa of the turbinates of freshly killed guinea pigs *in situ*. It was learned that: (1) Tap and distilled water when applied to the upper respiratory tract cause slowing of the ciliary beat; (2) 3% ephedrin hydrochlorid is not detrimental to ciliary activity but at times increases it slightly; (3) 5% cocain hydrochlorid is not detrimental to ciliary activity, but 10 and 20% solutions produce definite slowing, with good recovery; (4) mild silver protein in concentrations of 5, 10 and 20% produces an initial speeding of ciliary activity. This is followed by a slowing, which may be due to the water solvent rather than to the drug; (5) 0.5% eucalyptol has no deleterious effect on ciliary activity; (6) 0.5% menthol and, to a greater degree, 1% menthol have a mildly depressing effect on ciliary activity; (7) 1% thymol, 0.5% thymol and 1% eucalyptol, in the order named, are definitely detrimental to ciliary activity; (8) a 1 to 1000 solution of epinephrin hydrochlorid, 2% zinc sulphate and 2% mercurochrome, in the order named, are definitely detrimental to ciliary activity; (9) 0.5% silver nitrate is immediately and fatally detrimental to ciliary activity. In no instance was it possible to start the cilia beating again after its application.

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 PHYSIOLOGY
 

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## PROCEEDINGS OF

## THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF APRIL 16, 1934

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**Experiments on Chemotropism of Leukocytes.** MORTON McCUTCHEON and H. M. DIXON (Laboratory of Pathology, University of Pennsylvania). The chemotropic response of human polymorphonuclear leukocytes to different types of microorganisms was evaluated through experiments *in vitro*. Under the microscope the net distance was

measured by which each cell approached a clump of bacteria, and this distance was divided by the total length of the path of the cell. The resulting ratio is a measure of the chemotropic response, having as extreme values  $+1.00$  if the cell moves directly toward the bacteria,  $-1.00$  if the cell moves directly away from them. With staphylococci, streptococci, pneumococci, typhoid and tubercle bacilli; *Micrococcus tetragenus* and certain yeasts, mean ratios ranged only from  $+0.73$  to  $+0.86$ , indicating approximately equal attraction under these conditions. With the yeast, *Torula histolytica*, the ratio was  $+0.57$ . Control leukocytes, wandering in fields free from known chemotropic influence, gave a value of  $+0.07$ . With substances other than bacteria a wide range of values was obtained: gelatin,  $0.00$ ; dried blood,  $+0.18$ ; dried leukocytes,  $+0.25$ ; starch paste,  $+0.71$ .

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**The Present Status of the Coagulation Problem. An Experimental Review.** HARRY EAGLE (Laboratory of Bacteriology, University of Pennsylvania). The amount of thrombin formed in a mixture of plasma, platelets, Ca and fibrinogen is independent of the fibrinogen, and varies directly with the amount of the plasma factor (prothrombin). Platelets and cephalin accelerate thrombin production, but do not affect the total quantity formed. Treatment of horse thrombin with Na-oxalate does not affect its activity, although the Ca is precipitated quantitatively. This does not exclude the possibility that thrombin is a Ca-compound present in minute molecular concentration, but it does confirm the view of Hammarsten that Ca cannot be an intrinsic part of the fibrin molecule.

There is no simple linear relation between thrombin and fibrin. The quantitative relationships between the two and the rate of thrombin disappearance suggest that thrombin is an enzyme, as originally believed by Schmidt, rather than a stoichiometric component of the fibrin molecule. There is no significant change in the pH of the solution during the coagulation of fibrinogen by thrombin.

None of the four theories as to the reason for the fluidity of circulating blood (heparin, pro-prothrombin, platelet-stability, antithrombin) adequately explains the phenomenon. Heparin does not act by combining with prothrombin, but by retarding its transformation to thrombin. Platelets *in vitro* remain sufficiently intact in the presence of Ca to be readily centrifuged; and the sediment is quantitatively as active as the original platelet suspension. Thrombin injected intravenously in quantities less than that which would be liberated from the blood suffices to cause intravascular coagulation and death.

The retarded coagulation of hemophilic blood is not a platelet deficiency. Normal and hemophilic platelets accelerate thrombin production and coagulation to exactly the same degree. As originally believed by Addis, the deficiency lies in the prothrombin. Although present in normal concentration, it is transformed to thrombin by platelets and Ca more slowly than normal prothrombin.

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**Studies Concerning the Nutritional Value of Slightly Rancid Fat.** DOROTHY V. WHIPPLE (Department of Pediatrics, University of Pennsylvania). The chemical condition of the fat of a ration has been found

to be an important factor in determining the nutritional value of the ration.

Three comparable groups of rats were fed a fat-free basal diet adequate in all known dietary essentials. One group was given, in addition to the basal ration, 0.1 cc. daily of fresh neutral fat, the second group received 0.1 cc. daily of slightly rancid fat (peroxid value 15 to 20 millimols per kilo), and the third group was kept without any fat. The animals receiving the good fat grew normally and remained in apparently good health for the duration of the experiment (288 days). The animals in the fat-free group grew at a slower rate for the first  $5\frac{1}{2}$  months, then began to lose weight and finally died with symptoms of the fat deficiency disease described by Burr and Burr. The rats receiving the oxidized fat grew at about the same rate as the fat-free controls, and developed symptoms very similar to those of the fat deficiency disease in the same time period; their length of life, however, was longer than the fat-free animals.

A curative experiment was done in which comparable trios of animals suffering from severe fat deficiency disease were fed: (1) neutral fat; (2) partly oxidized fat; (3) no fat.

The animals receiving neutral fat were cured of the disease, those receiving no fat died, while those receiving oxidized fat died more quickly than the fat-free controls.

It is tentatively concluded that partly oxidized fat is unable to replace neutral fat in the diet, possibly due to the destruction of the double bonds in the nutritionally essential fatty acids; and that there may be a toxic factor produced in the fat by the oxidative process.

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**Studies on the Living Kidney Glomeruli of the Frog.** G. S. DE RENYI (Laboratory of Anatomy, University of Pennsylvania). Freshly isolated and fixed and stained preparations of the glomeruli of frog kidneys were examined microscopically. The following conclusions seem justified:

A. The small vessels in the glomerular tufts are true capillaries. Typical adventitial cells are attached to their outer surfaces. In a fresh condition these cells do not exhibit the property of contractility when stimulated mechanically.

B. The endothelium of the capillary loops differs in some respects from that in other capillaries.

C. The outer surface of the loops possesses no epithelial sheaths.

D. A gelatinous, highly viscid, optically homogeneous tissue covers the loops. This substance possesses a certain degree of elasticity, and contains cellular elements. In its physical properties it resembles the homogeneous matrix of connective tissue. It adheres to the walls of the loops and to their adventitial cells.

E. Since there is no epithelium upon the outer surface of the loops, epithelium plays no rôle in the filtration of urine. Only three structures are involved in the mechanism of urine formation: endothelium, a thin membrane, and a highly viscid, gelatinous tissue.

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**A Gonad-stimulating Extract from Alfalfa.** MAURICE H. FRIEDMAN and GERTRUDE S. FRIEDMAN (Laboratory of Physiology, University of Pennsylvania). For a variety of reasons it was thought very prob-

able that the pituitary gland did not elaborate its hormone from simple, widely distributed chemical substances, but required from the environment rather complex precursors (or active materials similar to the hormone) which were rather limited in distribution. If this were true, it was thought that the green plant would afford a likely source of such materials. Consequently alfalfa was subjected to a cold alkaline extraction and the resulting filtrate treated according to the Katzman-Doisy benzoic acid method for the extraction of the activity of pregnancy urine. The extracts so produced proved to be capable of stimulating the ovaries of the isolated rabbit, so that it can be said that alfalfa is capable of yielding a gonad-stimulating substance. Whether or not this fact has any direct physiological significance remains to be seen.

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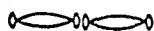
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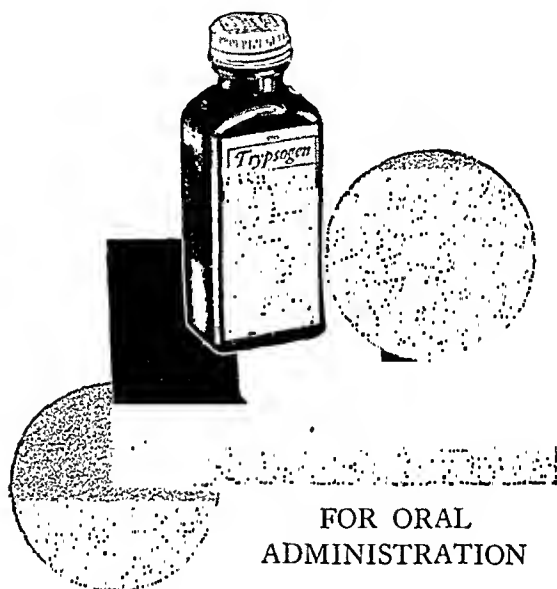
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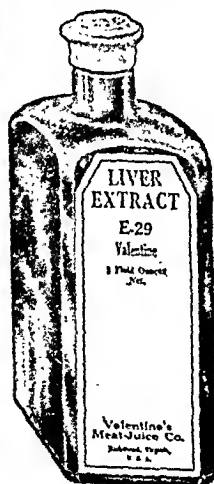
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<sup>1</sup> Science, 73, 243 (1931)

<sup>2</sup> Jour. Nutrition, 6, 179 (1933)

<sup>3</sup> Klin. Wochschr., 12, 1241 (1933)

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